Failure to initiate HIV treatment in patients with high CD4 counts: evidence from demographic surveillance in rural KwaZulu-Natal

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Running head: **Failure to initiate HIV treatment in patients with high CD4 counts**

Abstract

Objectives: To assess the relationship between CD4 count at presentation and ART uptake and assess predictors of timely treatment initiation in rural KwaZulu-Natal, South Africa.

Methods: We used Cox Proportional Hazards models to assess the association between first CD4 count and time from first CD4 to ART initiation amongst all treatment-naïve adults presenting to the Hlabisa HIV Treatment and Care Program between August 2011 and December 2012, with CD4<350 cells. For a sub-set of healthier patients (200≤CD4<350 cells) residing within the population surveillance of the Africa Health Research Institute, we assessed sociodemographic, economic, and geographic predictors hypothesized to influence ART uptake.

Results: 4,739 patients presented for care with eligible CD4 counts. The proportion initiating ART within six months of diagnosis was 67% (95% CI 63, 71) in patients with CD4≤50, 59% (0.55, 0.63) in patients with CD4 151-200, and 48% (95% CI 44, 51) in patients with CD4 301- 350. The hazard of starting ART fell by 17% (95% CI 14, 20) for every 100-cell increase in baseline CD4 count. Among healthier patients under demographic surveillance (n=193), observable sociodemographic, economic, and geographic predictors did not add discriminatory power beyond CD4 count, age, and sex to identify patients at high risk of non-initiation.

Conclusions: Individuals presenting for HIV care at higher CD4 counts were less likely to initiate ART than patients presenting at low CD4 counts. Overall ART uptake was low. Under new guidelines that establish ART eligibility regardless of CD4 count, patients with high CD4 counts may require additional interventions to encourage treatment initiation.

Key words: HIV, ART, failure to initiate, cascade of care, South Africa, demographic surveillance

Introduction

2015 World Health Organization (WHO) guidelines recommend HIV treatment for all HIV-infected individuals regardless of CD4 count (1). There are substantial benefits to early antiretroviral therapy (ART) initiation both for the patient's own health and for public health, as a result of the reduced transmission risk by patients with undetectable viral loads (2–7). However, in order to reach the high levels of ART coverage targeted by UNAIDS (8), large numbers of asymptomatic patients with high CD4 counts who were previously ineligible for ART must now accept and initiate treatment. If asymptomatic patients do not initiate ART, the full benefits of treatment as prevention will not be realized.

There is growing evidence of patients failing to initiate ART, even though they have linked to care and have been identified as eligible for treatment initiation (9–13). One reason proposed is that many patients believe they are "too healthy" to require ART. Previous studies have reported mixed results regarding the effect of health status on ART initiation. Some have found that healthier individuals are less likely to initiate treatment (14), and others have found that individuals presenting with advanced disease are more likely to die or be lost to follow up before ART initiation (15,16). These mixed findings may reflect heterogeneity across different settings and data limitations of standard clinical cohorts, which typically enroll patients at ART initiation, not at HIV testing. It is also possible that the relationship between health and ART uptake is non-monotonic: patients who are "too healthy" opt out of treatment, while those who are "too sick" may not survive long enough to start. Beyond health status at presentation, studies have suggested that age (17), gender (15,17), distance to clinic (18–20), living in rural areas (21), competing childcare obligations (22), education levels (12,23), financial security (18,24), and difficulty finding time off from work (16) may also influence uptake.

To better understand failure to initiate ART, we assessed predictors of ART uptake in rural South Africa. Using data on all patients diagnosed with HIV in the public sector HIV Treatment and Care Program in Hlabisa Sub-District, KwaZulu-Natal, we tested the hypothesis that among patients with ART-eligible CD4 counts (CD4<350), those with higher CD4 counts were less likely to initiate treatment. Exploiting the unique opportunity to link a sub-set of the clinical cohort to a population-based demographic and health surveillance system, we also examined a range of sociodemographic, economic and geographic predictors of failure to initiate ART to guide targeting of future interventions.

Methods

Ethics

Ethical approval for data collection, linkage, and analysis by the Africa Health Research Institute (AHRI) was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee. Verbal informed consent was obtained from household respondents. The analyses conducted for this paper consisted of secondary analysis of de-identified data and was determined "not human subjects research" by the Boston University Medical Campus IRB.

Data and study population

The Hlabisa HIV Treatment and Care Program provides public sector HIV care at 17 primary health clinics (PHCs) and one sub-district hospital in Hlabisa Sub-District in rural KwaZulu-Natal Province. The program was supported by the U.S. President's Emergency Program for AIDS Relief during the period of study (25). From 2004 through the end of 2013, clinical records were captured systematically in a database supported by the Africa Health Research Institute, which maintains a demographic and health surveillance system in the area. The cohort is extensively described elsewhere (25) and was one of the few clinical cohorts in sub-Saharan Africa to enroll patients at their first recorded CD4 count, usually performed at the time of HIV diagnosis, rather than at ART initiation. Patients eligible for ART attended three treatment literacy and counseling sessions prior to starting therapy. They were required to identify a treatment supporter and to sign an agreement to adhere before starting (25).

Since 2000, the Africa Health Research Institute has collected longitudinal sociodemographic data through biannual household survey visits, with response rates of greater than 99 percent (26), on a cohort of more than 100,000 people living in a 167-square-mile demographic surveillance area in northern KwaZulu-Natal. Socioeconomic and health information are included in the surveys annually; all households are geocoded and distances to nearest clinics have been calculated. About 40% of the Hlabisa HIV Treatment and Care Program catchment area population resides in the surveillance area. Clinical records have been linked at the individual level with the demographic surveillance using national identification numbers, full name, age, and sex (27,28).

The study population included all adults (≥ 18 years old) who received their first CD4 count between 11 August 2011 and 31 December 2012 in the Hlabisa HIV Treatment and Care Program and were eligible for ART under public sector guidelines (CD4 count ≤350). Patients who first presented for HIV care at the Hlabisa sub-District Hospital or at mobile

sites, rather than the PHCs in the program, were excluded, as were those whose age or gender could not be determined.

Outcome measures

The outcome of interest was the length of time from the date of an individual's first recorded CD4 count to the date that person initiated ART or end of follow-up. The analysis was restricted to patients whose first recorded CD4 count was ≤350 cells and thus eligible for ART. ART initiation data were collected until 31 December 2013, providing each individual in our study cohort with at least 12 months to initiate ART. Person-time was included from the date of an individual's first recorded CD4 count until the date that person initiated ART, died, or reached the end of the study period on 31 December 2013. For analysis of the population residing in the surveillance area, person-time was further censored when individuals moved away from their baseline place of residence.

Predictors of ART initiation

First recorded CD4 count (cells/mm^3), age (years), and sex were determined from the clinical database and available for the full study population. For the sub-sample of patients residing within the surveillance area, we collected data on a range of sociodemographic, economic and geographic characteristics that were potential predictors of ART uptake. We collected data on the distance from an individual's residence to the nearest clinic (coded as 0-2 km or >2km), and whether the residence was located in a rural or urban/peri-urban area.

Using data from the demographic surveillance, we calculated the number of children under six an individual had, and the number of household members that had linked to HIV care. Both were recoded as dichotomous indicators of having at least one child under six in the household and at least one household member linked to HIV care respectively. Socioeconomic status was assessed in the survey wave closest to the date of first CD4 count. Education was measured as the number of years of education received (1 to 15 years). We categorized patients as employed if they were employed or earning any income. Finally, using a principal component analysis of the responses from 53 survey questions regarding socio-economic status, we identified the 10 household assets most strongly correlated with household wealth and measured wealth as a count of how many of those assets an individual possessed. We imputed education and wealth for patients with missing data using the mean of the available sample. Dummy variables indicating observations with imputed values were included as controls during analysis.

Analytical approach

In order to determine if there is an association between individual health and the probability of starting treatment, we used survival analysis to assess the length of time from the date of an individual's first recorded CD4 count to the date that person initiated ART, stratified by baseline CD4 count. We produced Kaplan-Meier estimates of the likelihood of ART initiation within 6 months for each 50-cell CD4 count category. We repeated the analysis additionally stratifying by gender.

We then assessed the association between first CD4 count and the hazard of initiating ART using Cox proportional hazards models. We first estimated crude hazard ratios with CD4 counts alone. To assess whether the relationship between first CD4 count and initiation was confounded by other observable factors, we adjusted the model for age and sex, and in a third model, for age, sex, age-sex interactions, the year of the patient's first recorded CD4 count, and the clinic where the patient was registered. These covariates represent all baseline data available for the full Hlabisa sample on the date of patients' first CD4 counts. For each of these three covariate specifications, we modeled CD4 counts as a series of 50-cell CD4 categories and separately as a continuous predictor scaled so that a unit increase represents 100 cells/mm^3.

To identify persons most at risk of not initiating ART, we used Cox proportional hazards models to assess predictors of the initiation hazard for the sub-sample residing within the surveillance area. Due to the reduction in sample size, we included CD4 cell count using a continuous specification to preserve power. We estimated three predictive models, which were nested in order to evaluate whether the addition of covariates increased predictive power. We started with first CD4 count alone, and then added age, sex, and age*sex (the "age-sex-CD4" model). Lastly, we included all socioeconomic and geographic predictors described above to assess whether additional information on factors thought to influence uptake of ART but not regularly collected in clinical databases predicted non-initiation in our sample (the "all predictors" model). To assess whether the predictors were jointly significant, we conducted an F-test on the joint null hypothesis test that the coefficients on all socioeconomic and geographic predictors were equal to zero. We repeated this analysis for the sub-population under demographic surveillance with a first recorded CD4 count between 201 and 350 cells to explore whether predictors of initiation differed amongst healthier patients, a population targeted in current interventions.

Some patients may have died or out-migrated before they had the opportunity to initiate ART. Although the rate of death and outmigration is low in the six-month window following

clinical presentation which is the focus of our analysis, our results could be affected by coding these patients as having not initiated. To assess the robustness of our results, we considered death and outmigration as competing risks in our predictive regression model for the ACDIS cohort, censoring follow-up time at dates of death and/or out-migration.

Finally, we assessed the performance of the predictive models in identifying people at greatest risk of non-initiation. Specifically, we assessed whether the predicted probability of non-initiation would provide a useful "risk score" and evaluated whether a threshold rule on such a score would help identify patients to be targeted for future interventions to increase ART uptake. We used logistic models to predict the probability of ART initiation within six months for each patient under the "age-sex-CD4" model and under a series of adjusted models where we added socioeconomic and geographic predictors individually to the "age-sex-CD4" model based on what was found to be significant in the previous analysis. We then created indicators to identify patients at "high risk" for not starting ART, experimenting with thresholds set to target the 20%, 40%, 60% and 80% highest risk patients. For each threshold, we calculated the proportion of all true non-initiators identified as "high risk" by the risk score. We used repeated random sampling cross-validation techniques to prevent overfitting and estimate confidence intervals (described in Appendix). In assessing performance of our risk score, we note that a high-performing risk score would enable identification of a small group of "high risk" patients representing a large proportion of the patients who in fact would fail to initiate ART. We compared the results across different models to assess the benefit of including sociodemographic, economic, and geographic predictors in our model, in addition to CD4, age and sex.

Results

Table 1 presents descriptive statistics for the full sample, the sub-population of patients residing within the surveillance area, and for healthier patients residing in the surveillance area (200<CD4≤350). Of the 4,630 patients presenting for care between 2011 and 2012 with eligible CD4 counts, 2,786 (60%) initiated ART within the study period, amongst whom 2,626 (57%) and 2,730 (59%) initiated within 6 months and 1 year of their first recorded CD4 count respectively. Thirty-seven patients were excluded because either their age or gender was not reported. Amongst those who initiated ART, over 95% of patients did so at the same clinic where they received their first CD4 count, rather than at one of the other 16 clinics in the area, suggesting a fair amount of stability in the six-month follow-up period (Appendix, Table 5). Of the 434 patients residing within the surveillance area, 320 (74%) initiated ART within the study period, amongst whom 300 (69%) and 312 (72%) initiated within 6 months

and 1 year of their first recorded CD4 count. These rates were lower in the healthier sub-set of patients (n=193), of whom 113 (59%) and 121 (63%) initiated ART within 6 months and 1 year respectively.

(Table 1)

Figure 1 shows the Kaplan-Meier likelihood of initiating ART within 6 months by first recorded CD4 count. Whilst the sickest individuals (CD4≤50) had a 67% (95% CI 63, 71) chance of initiating ART within 6 months, the probability of initiating ART decreased approximately linearly by an average of 3 percentage points for every 50-cell count increase. 48% (95% CI 44, 51) of patients with first CD4 counts 301-350 initiated ART (Appendix Table 1). These trends did not differ by sex (Appendix Figure 1).

(Figure 1)

Table 2 presents hazard ratios of ART initiation associated with each predictor in the full sample. The hazard of ART initiation fell by 17% (95% CI 14, 20) for every 100-cell increase in baseline CD4 count, with CD4 count modeled continuously. These effects were robust to alternate specifications controlling for age, sex, age sex interactions, year of first recorded CD4 count, and clinic fixed effects. Conditional on other covariates, rates of ART initiation were lowest among younger patients. No differences were observed by sex.

(Table 2)

Table 3 presents hazard ratios of ART initiation associated with predictors in the sub-population of residents within the surveillance area and in surveillance residents with higher CD4 counts. In the all-CD4 count sample, patients with higher CD4 counts were less likely to initiate ART. The initiation hazard fell by 25% (95% CI 0.68-0.84) for every 100-cell increase in CD4 count. After adjusting for age, sex, first recorded CD4 cell count and age-sex interactions, we identified predictors of non-initiation including living over 2km away from the nearest clinic (HR 0.80, 95% CI 0.64-0.998), living in a rural area (HR 0.77, 95% CI 0.62-0.96), and having children under the age of 6 (HR 0.74, 95% CI 0.56-0.97).

In the healthier sub-population, none of the predictors had a statistically significant association with ART initiation in either the crude, adjusted, or fully mutually adjusted models. However, effect sizes for distance to clinic, rural, and children under 6 were similar

to those observed in the full resident population. Considering death and outmigration as competing risks did not substantially change the results (Appendix, Table 6).

(Table 3)

Using a logistic model (Appendix, Table 3), we estimated the probability of ART initiation within 6 months for each patient under the "age-sex-CD4" model and "all predictors" model and assessed the distribution of predicted probabilities by actual initiation status (Appendix, Figure 2). As expected, predicted probabilities of non-initiation are higher among those who in fact did not initiate (termed "true non-initiators" below).

Figure 2 plots the percentage of true non-initiators identified by the "age-sex-CD4" model and a series of models augmenting the former with socioeconomic and geographic variables that were significant predictors in the previous analysis (number of children under 6, distance to the nearest clinic, rural). We report the percent of true non-initiators identified if 20%, 40%, 60%, or 80% of patients were determined to be "high risk" for non-initiation. Targeting interventions to increase ART uptake on the basis of age, sex, and first CD4 count would substantially improve targeting over an intervention allocated at random (the 45-degree line). However, screening for potential non-initiators using a wide range of socioeconomic and geographic predictors did not outperform the simple screening tool using age, sex, and CD4 count. In general, discriminatory power was rather low. 40% of all patients would have to be targeted with an intervention in order to reach 58% of would-be non-initiators. 80% of all patients would have to be targeted to reach 90% of non-initiators.

(Figure 2)

Discussion

Treating all persons infected with HIV regardless of CD4 count is likely our best way to reduce morbidity and mortality and curtail the spread of HIV. Yet uptake of ART among patients diagnosed with HIV and eligible for ART is far from universal. In a large prospective cohort in rural South Africa, we found that only 57% of patients with an eligible CD4 count (<350) initiated ART within six months, in spite of treatment being available for free at point of service. Why do patients not initiate ART?

Within the population that was eligible for ART at a threshold of 350 CD4 cells/mm^3, healthier patients were much less likely to initiate ART than patients presenting with low CD4 counts. Initiation probabilities fell from 67% (CD4 0-50 cells/mm^3) to 48% (CD4 300-350 cells/mm^3), a gap of nearly 20 percentage points. The relationship was approximately linear, precisely estimated, and robust to adjustment for age, sex, and other baseline covariates. This is some of the first quantitative evidence on the association between CD4 count at presentation and ART uptake (13–16), confirming evidence in qualitative studies (29).

Reasons for failing to initiate treatment have been identified on both the patient and provider sides. On the provider side, multiple required visits, long waiting times, stock outs of supplies, staff absences, and poor communication between staff and patients all deter treatment initiation(9,30–32). Patients themselves face barriers ranging from stigma and fear of disclosure to the costs of clinic visits and the risk of wage loss(29,30,33). In quantitative studies, variables associated with failing to start treatment include age (17), gender (15,17), distance to clinic (18–20), living in rural areas (21), competing childcare obligations (22), education levels (12,23), financial security (18,24), and difficulty finding time off from work (16). Feeling healthy may both reinforce a patient's other reasons for avoiding initiation and constitute a reason in itself.

A number of approaches to increase ART uptake among eligible patients have shown promise(34). In a randomized trial in Johannesburg, South Africa, initiating patients on ART on the same day as HIV diagnosis sharply reduced loss to follow up before ART initiation and led to an overall increase in viral suppression among patients eligible for treatment(35). Trials in Uganda(36), China(37), and the United States(38) all found that simplifying the process of treatment initiation improves ART uptake. Improved counseling was associated with very high uptake in Cape Town, South Africa in a pilot project(39). Other potentially effective approaches include financial incentives to remain in care(40), active tracing of patients who do not return to start ART, and home-based treatment initiation(41).

The challenge for national HIV programs will be to allocate resources to encourage relatively healthy HIV patients to initiate ART without diminishing investment in those with low CD4 counts who must start treatment immediately. We found that first eligible CD4 count was the most valuable predictor of ART non-initiation. Nevertheless, reallocating resources towards patients with high CD4 counts could crowd out sicker patients to the detriment of overall health outcomes (42). To avoid such unintended consequences, health systems have prioritised the sickest patients for faster initiation(43). Ideally patients at risk of non-initiation and who might benefit from interventions could be targeted in advance. Beyond CD4 count,

age and sex, neither commonly available clinical variables nor socioeconomic and geographic characteristics thought to influence uptake had any effect at all on our ability to identify high risk patients, however.

Our study had several limitations. First, the size of the sub-population residing in the demographic surveillance and seeking care with CD4 counts between 200 and 350 cells was only n=193. This small population size limited our power to detect statistically significant socioeconomic predictors of non-initiation. On the other hand, the point estimates did not suggest very large effects, and including additional variables beyond CD4, age, and sex did not increase the discriminatory power of the predictive model to identify patients at high risk of failure to initiate ART. Second, ART uptake was in general higher among residents of the population surveillance area compared to the full Hlabisa Cohort. One explanation is that this analysis was limited to residents, whereas the full Hlabisa cohort may have included patients passing through and not residing in the catchment area. It is also possible that the AHRI's continuous demographic surveillance and community health education efforts led to higher uptake. In any case, the generalizability of our predictive models is limited. Third, it is possible that we are underestimating ART uptake due to private sector care-seeking and out-migration to other health catchment areas. However, private sector utilization for ART is low in this setting and out-migration is unlikely to be a major factor in a six-month initiation window. Fourthly, the patients in our sample were limited to those who were eligible for ART under earlier guidelines. It is possible that the results we report will not apply to patients with CD4 counts above 350, who are all now eligible for ART under September 2016 revisions to South Africa's national guidelines. Finally, some patients – particularly those presenting with low CD4 counts – may have died before they had the opportunity to start ART. Our analysis coded these patients (accurately) as having not started ART. Treating death and outmigration as competing risks for ART initiation yielded similar results. This was confirmed in analysis of the ACDIS subsample, where death and outmigration could be reliably estimated.

If healthier patients are significantly less likely to start ART than sicker patients, implementation of WHO recommendations to offer ART to all patients at HIV diagnosis may have less impact than hoped. Our results suggest that increasing treatment coverage to levels necessary to stop HIV transmission may be more difficult than has been reflected in models of "test and treat" (44,45). Success will depend not just on expanding treatment eligibility to asymptomatic patients, but also on rethinking how care is provided to healthy patients and how to increase demand for early ART. We have shown that targeting initiation support interventions based on easily-collected socioeconomic and geographic factors is

unlikely to be a solution. CD4 count remains highly predictive and potentially could be used to stratify care from diagnosis until patients are established on ART. Further research to better understand how to increase initiation among patients with high CD4 counts – in real world clinical settings and at scale – is critical to achieving the reductions in transmission necessary to bring about the end of the epidemic.

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Tables

See attachment.

Figures and figure captions

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References

1. WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015.
2. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493–505.
3. Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 Jul;373(9):795–807.
4. Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, Ouassa T, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015 Jul;373(9):808–22.
5. Bor J, Moscoe E, Mutevedzi P, Newell M-L, Bärnighausen T. Regression Discontinuity Designs in Epidemiology. Epidemiology [Internet]. 2014;25(5):729–37. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00001648-201409000-00016

6. Bor J, Moscoe E, Bärnighausen T. When to Start HIV Treatment: Evidence from a Regression Discontinuity Study in South Africa. In: Population Association of America Annual Meeting. San Diego, CA; 2015.
7. Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell M-L. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science. 2013;339(6122):966–71.
8. UNAIDS. 90-90-90 An ambitious treatment target to help end the AIDS epidemic. Http://WwwUnaidsOrg/Sites/Default/Files/Media_Asset/90-90-90_En_0Pdf. 2014;40.
9. Micek MA, Gimbel-Sherr K, Baptista AJ, Matediana E, Montoya P, Pfeiffer J, et al. Loss to follow-up of adults in public HIV care systems in central Mozambique: identifying obstacles to treatment. J Acquir Immune Defic Syndr [Internet]. 2009;52(3):397–405. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2784145&tool=pmcentrez&rendertype=abstract
10. Shastri S, Sathyanarayna S, Nagaraja SB, Kumar AM V, Rewari B, Harries AD, et al. The journey to antiretroviral therapy in Karnataka, India: Who was lost on the road? J Int AIDS Soc. 2013;16:1–6.
11. Aliyu MH, Blevins M, Parrish DD, Megazzini KM, Gebi UI, Muhammad MY, et al. Risk factors for delayed initiation of combination antiretroviral therapy in rural north central Nigeria. J Acquir Immune Defic Syndr [Internet]. 2014;65(2):e41-9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3818360&tool=pmcentrez&rendertype=abstract
12. McGrath N, Glynn JR, Saul J, Kranzer K, Jahn A, Mwaungulu F, et al. What happens to ART-eligible patients who do not start ART? Dropout between screening and ART initiation: a cohort study in Karonga, Malawi. BMC Public Health [Internet]. BioMed Central Ltd; 2010;10(1):601. Available from: http://www.biomedcentral.com/1471-2458/10/601
13. Plazy M, Dray-Spira R, Orne-Gliemann J, Dabis F, Newell ML. Continuum in HIV care from entry to ART initiation in rural KwaZulu-Natal, South Africa. Trop Med Int Heal. 2014;19(6):680–9.
14. Odeny TA, DeCenso B, Dansereau E, Gasasira A, Kisia C, Njuguna P, et al. The clock is ticking: The rate and timeliness of antiretroviral therapy initiation from the time of treatment eligibility in Kenya. J Int AIDS Soc. 2015;18(1):1–8.
15. Togun T, Peterson I, Jaffar S, Oko F, Okomo U, Peterson K, et al. Pre-treatment mortality and loss-to-follow-up in HIV-1, HIV-2 and HIV-1/HIV-2 dually infected patients eligible for antiretroviral therapy in The Gambia, West Africa. AIDS Res Ther [Internet]. BioMed Central Ltd; 2011;8(1):24. Available from:

http://www.aidsrestherapy.com/content/8/1/24

16. Bassett I V, Wang B, Chetty S, Mazibuko M, Bearnot B, Giddy J, et al. Loss to care and death before antiretroviral therapy in Durban, South Africa. J Acquir Immune Defic Syndr. 2009;51(2):135–9.
17. Pepper DJ, Marais S, Wilkinson RJ, Bhaijee F, de Azevedo V, Meintjes G. Barriers to initiation of antiretrovirals during antituberculosis therapy in Africa. PLoS One. 2011;6(5):2–7.
18. Layer EH, Kennedy CE, Beckham SW, Mbwambo JK, Likindikoki S, Davis WW, et al. Multi-level factors affecting entry into and engagement in the HIV continuum of care in Iringa, Tanzania. PLoS One. 2014;9(8).
19. Wachira J, Naanyu V, Genberg B, Koech B, Akinyi J, Kamene R, et al. Health facility barriers to HIV linkage and retention in Western Kenya. BMC Heal Serv Res [Internet]. 2014;14(December):646. Available from: http://www.biomedcentral.com/content/pdf/s12913-014-0646-6.pdf
20. Kunihira NR, Nuwaha F, Mayanja R, Peterson S. Barriers to use of antiretroviral drugs in Rakai district of Uganda. Afr Health Sci. 2010;10(2):120–9.
21. Alvarez-Uria G, Pakam R, Midde M, Naik PK. Predictors of delayed antiretroviral therapy initiation, mortality, and loss to followup in HIV infected patients eligible for HIV treatment: data from an HIV cohort study in India. Biomed Res Int [Internet]. 2013;2013:849042. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3830789/?tool=pubmed%5Cnhttp://dx.doi.org/10.1155/2013/849042
22. Parrott FR, Mwafulirwa C, Ngwira B, Nkhwazi S, Floyd S, Houben RMGJ, et al. Combining qualitative and quantitative evidence to determine factors leading to late presentation for antiretroviral therapy in malawi. PLoS One. 2011;6(11).
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 [Internet]. 2012;7(5):e37125. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22615917%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3352894
24. Mshana G, Wamoyi J, Busza J. Barriers to accessing antiretroviral therapy in Kisesa, Tanzania: a qualitative study of early rural referrals to the national program. AIDS Patient Care …. 2006;20(9):649–57.
25. Houlihan CF, Bland RM, Mutevedzi PC, Lessells RJ, Ndirangu J, Thulare H, et al. Cohort Profile: Hlabisa HIV Treatment and Care Programme. Int J Epidemiol. 2011 Apr;40(2):318–26.
26. Tanser F, Hosegood V, Bärnighausen T, Herbst K, Nyirenda M, Muhwava W, et al.

Cohort profile: Africa centre demographic information system (ACDIS) and population-based HIV survey. Int J Epidemiol. 2008;37(5):956–62.

27. Bor J, Bärnighausen T, Newell C, Tanser F, Newell ML. Social exposure to an antiretroviral treatment programme in rural KwaZulu-Natal. Trop Med Int Heal. 2011;16(8):988–94.
28. Bor J, Tanser F, Newell M-L, Bärnighausen T. In a study of a population cohort in South Africa, HIV patients on antiretrovirals had nearly full recovery of employment. Health Aff. 2012 Jul;31(7):1459–69.
29. Katz IT, Dietrich J, Tshabalala G, Essien T, Rough K, Wright AA, et al. Understanding treatment refusal among adults presenting for HIV-testing in Soweto, South Africa: a qualitative study. AIDS Behav [Internet]. 2015;19(4):704–14. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4393756&tool=pmcentrez&rendertype=abstract
30. Govindasamy D, Ford N, Kranzer K. Risk factors, barriers and facilitators for linkage to ART care in sub-Saharan Africa: a systematic review. AIDS. 2012 Jul;26(March):2059–67.
31. Scott V, Zweigenthal V, Jennings K. Between HIV diagnosis and initiation of antiretroviral therapy: assessing the effectiveness of care for people living with HIV in the public primary care service in Cape Town, South Africa. Trop Med Int Heal. 2011 Jul;16(0):1384–91.
32. Siedner MJ, Lankowski A, Haberer JE, Kembabazi A, Emenyonu N, Tsai AC, et al. Rethinking the "'Pre'" in Pre-Therapy Counseling: No Benefit of Additional Visits Prior to Therapy on Adherence or Viremia in Ugandans Initiating ARVs. PLoS One. 2012;7(6):e39894.
33. Chimbindi N, Bor J, Newell M-L, Tanser F, Baltussen R, Hontelez J, et al. Time and Money: The True Costs of Health Care Utilization for Patients Receiving "Free" HIV/Tuberculosis Care and Treatment in Rural KwaZulu-Natal. J Acquir Immune Defic Syndr. 2015 Oct;70(2):e52-60.
34. Rosen S, Fox MP, Larson B, Sow PS, Ehrenkranz PD, Venter F, et al. Accelerating the uptake and timing of antiretroviral therapy initiation in sub-Saharan Africa: an operations research agenda. PLoS Med. 2016;In press.
35. Rosen S, Maskew M, Fox MP, Nyoni C, Mongwenyana C, Malete G, et al. Initiating Antiretroviral Therapy for HIV at a Patient's First Clinic Visit: The RapIT Randomized Controlled Trial. PLoS Med. 2016;13(5):e1002015.
36. Amanyire G, Semitala FC, Namusobya J, Katuramu R, Kampiire L, Wallenta J, et al. Streamlining Antiretroviral Therapy Uptake: A Stepped-Wedge Cluster Randomized Trial. CROI 2016.

37. Wu Z, Zhao Y, Ge X, Mao Y, Tang Z, Shi CX, et al. Simplified HIV Testing and Treatment in China: Analysis of Mortality Rates Before and After a Structural Intervention. PLOS Med. 2015;12(9):e1001874.
38. Highleyman L. Same - day start to antiretroviral treatment leads to faster HIV suppression in San Francisco. AIDSMap News. 2015;(Ias).
39. Wilkinson L, Duvivier H, Patten G, Solomon S, Mdani L, Patel S, et al. Outcomes from the implementation of a counselling model supporting rapid antiretroviral treatment initiation in a primary healthcare clinic in Khayelitsha , South Africa. South African J HIV Med. 2015;16(1):1–7.
40. Bassett I V, Wilson D, Taaffe J, Freedberg KA. Financial incentives to improve progression through the HIV treatment cascade. Curr Opin HIV AIDS. 2015;451–63.
41. MacPherson P, Lalloo DG, Webb EL, Maheswaran H, Choko AT, Makombe SD, et al. Effect of optional home initiation of HIV care following HIV self-testing on antiretroviral therapy initiation among adults in Malawi: a randomized clinical trial. JAMA. Jan;312(4):372–9.
42. Bärnighausen T, Bloom DE, Humair S, Waning B, Kaplan W, Fox M, et al. Human Resources for Treating HIV/AIDS: Are the Preventive Effects of Antiretroviral Treatment a Game Changer? Fox MP, editor. PLoS One. Public Library of Science; 2016 Oct;11(10):e0163960.
43. Kluberg SA, Fox MP, LaValley M, Pillay D, Bärnighausen TW, Bor J. Do ART eligibility expansions crowd out the sickest? Evidence from South Africa. In: Conference on Retroviruses and Opportunistic Infections (CROI). Boston, MA; 2016.
44. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet [Internet]. Elsevier; 2009 Jul 16;373(9657):48–57. Available from: http://dx.doi.org/10.1016/S0140-6736(08)61697-9
45. Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E, Bershteyn A, et al. HIV treatment as prevention: Systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. PLoS Med. 2012;9(7).