Background
In a collaboration with the national Ministry of Health in Malawi, Médecins Sans Frontières (MSF) has been providing free HIV care and antiretroviral therapy in Chiradzulu, a district of 270,000 inhabitants, since 2001. The HIV prevalence was 17% of the population aged 15-59 years in 2013 (Maman D, JIAS 2016).

New WHO guidelines for universal test and treat imply many will start antiretroviral therapy (ART) without symptoms. A critical question is whether patients who initiate ART at high CD4 counts achieve good retention in care while on ART in sub-Saharan Africa.

Malawi has implemented the prevention of mother to child transmission (PMTCT) B+ programs since 2011. In addition, a growing number of males with advanced AIDS disease, tuberculosis, and Kaposi sarcoma are starting ART at CD4 counts above 350 and 500 cells/µl. We assessed in Chiradzulu project the association between high CD4 count at ART initiation, and subsequent retention and survival.

Objectives

To identify whether ART initiation at CD4 count ≥ 500 cells/µl is associated with a better retention in care and survival than when initiated at lower CD4 count categories.

To identify risk factors underlying the hypothesis that men and women starting ART at CD4 count ≥ 500 cells/µl have better retention and survival than those with lower CD4 count categories.

Methods

Design
2011-2015 retrospective observational cohort study using routine program data.

Study Population
All adults ≥ 15 years old who started ART between 2011 and 2015 in Chiradzulu.

Lost to follow-up was defined as 9 months after a clinic visit without contact, being dead or transferred out. Normal follow-up was 6 monthly visits.

Primary outcome: death, a binary variable with date recorded by MSF staff. Secondary outcome: attrition, defined as lost to follow-up 9 months after a clinic visit, or the date of death. Attrition included lost to follow-up or death who died.

Statistical Analyses

All analyses were conducted by gender, with mortality rates and 95% confidence intervals (CIs) calculated. The Kaplan-Meier survival curves were used to describe the survival of ART patients. The log-rank test was used to compare survival between males and females. Cox regression models were used to assess the association of patients’ characteristics with survival.

D MULTIVARIATE ANALYSIS
Retention in care was associated with CD4 count at ART initiation (Log Rank Test, p<0.001). Males and females had statistically significant different retention attrition profiles over time. Attrition was higher for men with ≥ 500 cells/µl but had the lowest retention curve, even if it remained above 60% (Table 1).

In the multivariate analysis, women with CD4 ≥ 500 cells/µl had a lower retention in care than men who initiated between 350-499 (OR 0.72; 95%CI 0.54-0.95) and 200-349 (OR 0.82; 95%CI 0.71-0.95). Similar trends were observed for men but the differences were not statistically significant (≥ 350 vs 350-499 OR 0.84; 95%CI 0.62-1.14).

Table 1: Multivariate Cox Regression analysis of retention in care for females and males, Chiradzulu, Malawi, 2011-2015

Results

A STUDY INCLUSION

Of the 21,705 patients aged ≥ 15 years old who initiated ART between 2011-2015, 15,260 (66.7% females and 63.37% males) had a CD4 count at initiation. In males the CD4 count repartition was: 239 (3.8%) CD4 ≥ 500 cells/µl, 2,269 (10.9%) CD4 350-499, 644 (3.3%) CD4 200-349, 3,239 (37.3%) CD4 200-394, and 3,025 (48.5%) CD4 <200 cells/µl. In females, 1,393 (13.9 %) had CD4 ≥ 500 cells/µl, 787 (17.8%) CD4 350-499, 4,079 (40.7%) CD4 200-349, and 2,410 (24.8%) CD4 <200 cells/µl.

At ART initiation, males presented the following characteristics: median CD4 count was 206 cells/µl (IQR 102-306); median age at ART start was 38 years (IQR 33.4-45); 3,866 (62.7%) had a WHO staging of 1 or 2 at initiation, median BMI of 19.86 kg/m2 (IQR 18.29-21.53) and the majority was included in 2012. Among females, the median CD4 count was 288 cells/µl (IQR 188-407), the mean age was 33 (IQR 28-41), 7,640 (77.1%) had a WHOD staging of 1 or 2, and the median BMI was 21.36 kg/m2 (IQR 19.31-23.53).

At end of follow-up, 12,767 (78.7%) patients were still in care, 2,538 (15.6%) were lost to follow-up,302 (1.9%) were transferred out, and 661 (4.1%) were dead. Among males, 1,114 (1.7%) were lost to follow-up, 355 (0.5%) died, 106 (1.6%) were transferred out, and 4,662 (74.7%) were still followed-up. Among females, 1,424 (14.2%) were lost to follow-up, 308 (3.1%) were dead, 196 (2.5%) were transferred out, and 8,096 (80.8%) were still followed up.

B SURVIVAL

661 deaths were observed over a total analysis time at risk of 36,387.69 person years. In people ≥ 200 cells/µl, 5 deaths were recorded among males, and 19 among females. Mortality rates were higher for men (9.15% vs 8.82% (p=0.05) and women (9.12% vs 8.82% (p=0.03)). The mortality rate was respectively 9.0 p100p and 3.9 p100p among males and females was 90% at 5 years across all CD4 categories as illustrated with the Kaplan Meier curves, (Fig 1).

Discussion

This study shows that low retention in care is achieved in females and males with high CD4 count at ART initiation, even if 80% of the study population was still in care after 5 years. The effect of CD4 at initiation on mortality and retention is modified by age, WHO staging and BMI at start. Other studies in resource limited settings have found a higher risk of loss to follow-up for the two first years on ART in patients in option B+ (Haas AD, Lancet 2016; Tenthani L, AIDS 2014, Mutasa-Apato, PLoS One 2014).

Strengths: to our knowledge, this is the first time attrition outcomes at high CD4 counts, over 48 months, issued from a large Sub-Saharan African retrospective cohort study, are reported.

Limitations: losses and death to follow-up were classified together as attrition, and were not analyzed as correlated data. This might have overestimated attrition, especially during the first year on ART. There might be a correlation between CD4 at ART initiation, BMI and WHO staging, which has not been taken into account in this analysis. The analysis was not fully adjusted on time on ART. We could not differentiate retention among pregnant and non-pregnant women.

Generalization: The limited number of deaths in the high CD4 count categories limits the generalizability of the survival analysis. The study was relatively small, with few males starting ART with CD4 ≥500 cells/µl. Our findings are expected to be generalizable for Sub-Saharan African countries, but not for high income countries.

Conclusion: initiating ART at CD4 ≥ 500 cells/µl was associated with lower retention in care compared to those who initiated ART between 350-499 cells/µl. Even if these results come mainly from women on PMTCT B+, in the treat-all era, specific attention to those initiating at high CD4 is needed to ensure good retention.

Acknowledgements
Chiradzulu Community, MSF team and study participants, Epicentre, J. Bon Ferhat