Lower retention in care when ART are initiated with CD4≥500 cells /ml

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Background

- In 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 initiated 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 under 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 district.

- 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. **Main 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 includes lost to follow-up and people who died. Patients were censored if transferred out, or at the 31st December 2015. **Exposure**: CD4 at initiation as 4-categories variable. **Risk factors studied**: age , Body Mass Index, WHO staging, as categorical variables

Procedures

All analysis was stratified by gender, with mortality rates and 95% confidence intervals (CI). The following CD4 categories were used: 0-199, 200-349, 350-499, ≥ 500 cells/µl . Kaplan Meier survival and retention curves by CD4 at initiation were drawn. Nelson Aalen curves were drawn to assess departure from the proportional hazard assumption. Multivariate Cox regression models obtained hazard ratios (HR) to show the effect of CD4 at initiation on mortality and retention, adjusted for WHO staging, Body Mass index, and age, which were identified as potential confounders or effect modifiers.
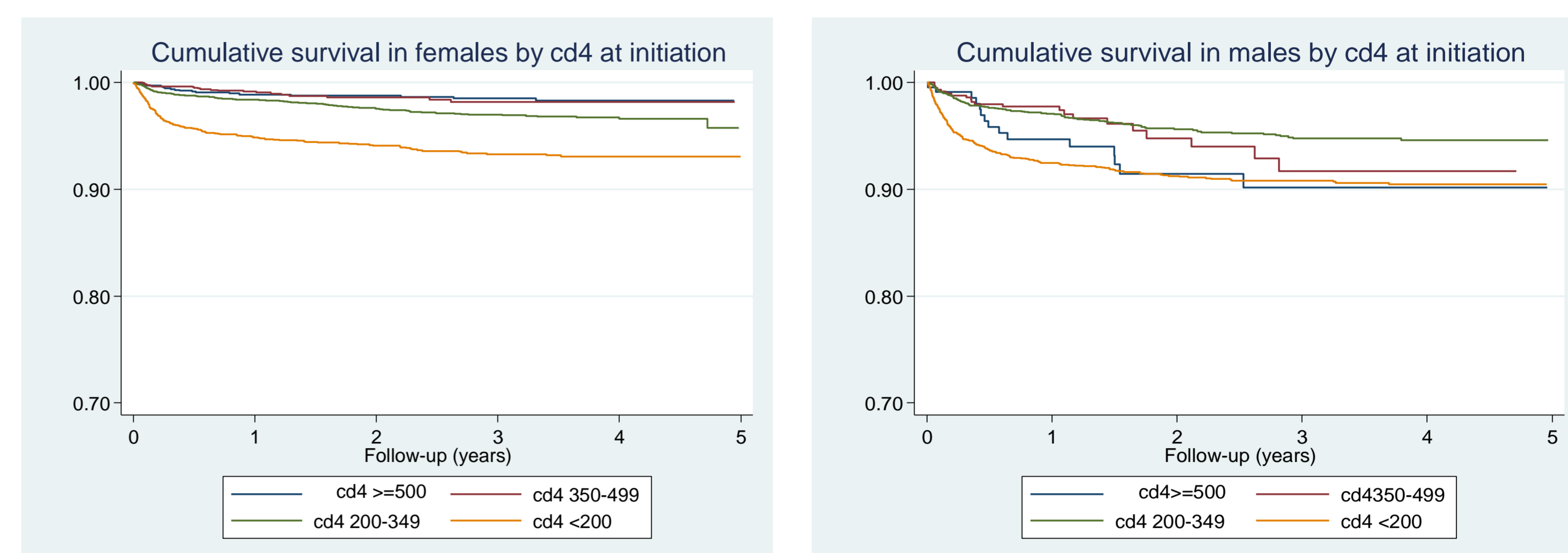
Results

A/ STUDY INCLUSION

- Of the 21,705 patients aged ≥ 15 years old who initiated ART between 2011-2015, 16,258 (10,021 females and 6,237 males) had a CD4 count at initiation. In males the CD4 count repartition was: 239 (3.8%) CD4 ≥ 500 cells/µl , 644 (10.3%) CD4 350-499, 2,329 (37.3%) CD4 200-349; and 3,025 (48.5%) CD4 <200 cells/µl . In females, 1,393 (13.9 %) had CD4 ≥ 500 cells/µl , 1,787 (17.8%) CD4 350-499, 4,079 (40.7%) CD4 200-349, and 2,762 (27.6%) 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 [IQR 32-45] , 3,868 (62.7 %) had a WHO staging of 1 or 2 at initiation, median BMI of 19.88 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 WHO staging of 1 or 2, and the median BMI was 21.33 kg /m2 [IQR 19.31-23.53]

- At end of follow-up, 12,757 (78.5%) 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 (17.9%) were lost to follow-up, 355 (5.7%) were dead, 106 (1.7%) were transferred out, and 4,662 (74.7%) were still followed-up. Among females, 1,424 (14.2%) were lost to follow-up, 306 (3.1%) were dead, 196 (2.0%) were transferred out, and 8,095 (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 with CD4 ≥ 500 cells/µl, 5 deaths were recorded among males, and 19 among females. Mortality rates were higher for men (2.8p100 person year (95%CI: 2.5-3.1) than for women (1.3p100 person-year (95%CI: 1.2-1.4)). Survival estimates 48 months after initiation were similar between patients with baseline CD4 ≥ 500 cells/µl and 350-499 cells/µl , for both women (98.3% vs 98.1%, p=0.95) and men (91.2% vs 92.0%, p=0.33). The mortality rate was respectively 9.0 p100py and 3.9 p100py among males and females during the first 6 months on ART. The cumulative survival in males and females was above 90% at 5 years across all CD4 categories as illustrated with the Kaplan Meier curves, (Fig 1).
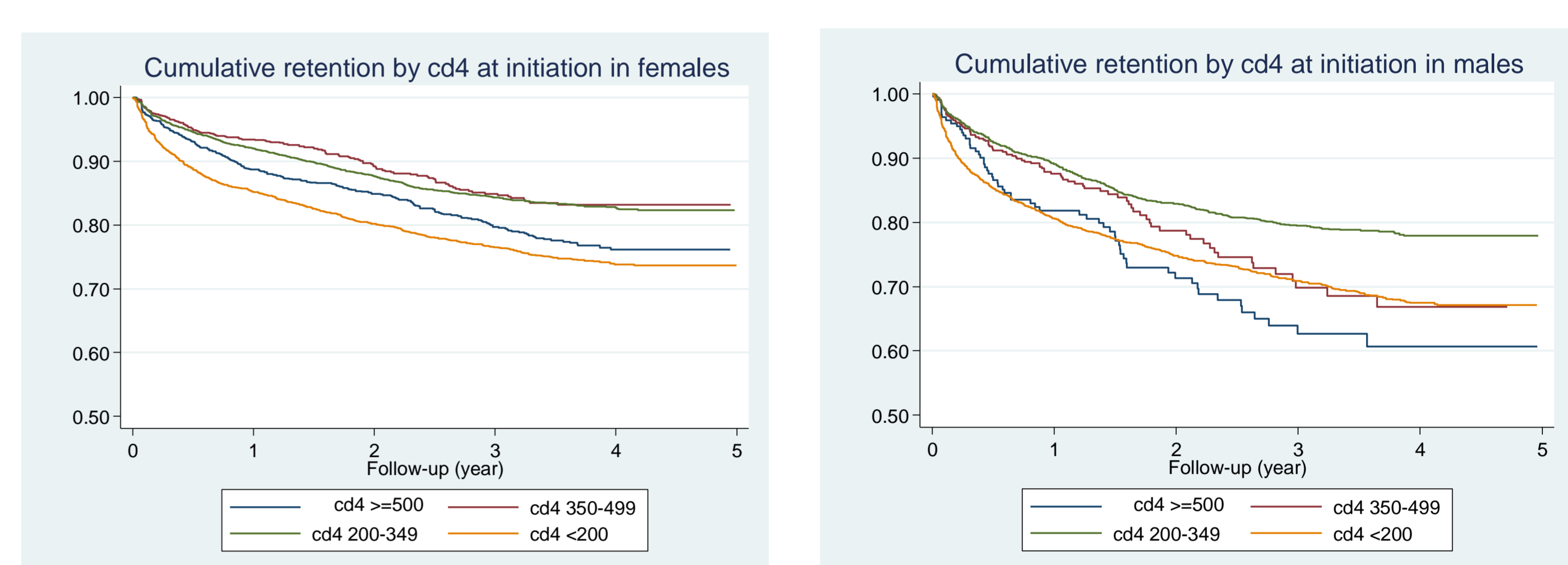
Figure 1: Kaplan –Meier estimates of survival probabilities in females and males according to CD4 count at initiation, Chiradzulu, Malawi, 2011-2015.

C/ RETENTION IN CARE

- Retention in care 48 months after ART initiation was 75.4% , 82.1%, 81.9%, and 72.1% among women with initial CD4 at ≥ 500, 350-499, 200-349, and <200 cells/µl (Log Rank Test, p<0.01) respectively.

Figure 2: Kaplan-Meier retention curves stratified by gender and CD4 at initiation, Chiradzulu, Malawi, 2011-2015.

- Attrition was associated with CD4 count at ART initiation (Log Rank Test, p<0.001). Males and females had statistically significant different attrition profiles over time. Attrition was higher during the two first years on ART. Males with CD4 ≥ 500 had the lowest retention curves, even if it remained above 60%. By contrast, in females, the lowest retention curves were observed in the CD4 category< 200 and ≥ 500 cells/µl, while remaining above 70% (Fig 2).

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 profiles over 5 years post ART initiation. Males with CD4 count at ≥ 500 cells/µl had the lowest retention curve, even if it remained above 60% (Table 1).

- In the multivariate analysis, women with CD4 ≥ 500cells/µl had a lower retention in care than those who initiated between 350-499 (aHR 0.72; 95%CI 0.60-0.88) and 200-349 (aHR 0.82; 95%CI 0.71-0.95). Similar trends were observed for men but the differences were not statistically significant (≥ 500 vs 350-499 aHR 0.84; 95%CI 0.62-1.14).

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

Variable	Adjusted hazard ratio (95%CI)	p-value	Adjusted hazard ratio (+95%CI)	p-value
Gender	Female		Males	
CD4 (cell/µl)				
≥500	1	<0.001	1	<0.001
350-499	1.54 (1.43-1.65)		1.51 (1.29-1.75)	
200-349	0.79 (0.74-0.84)		0.71 (0.61-0.81)	
<200	0.81 (0.75-0.86)		0.75 (0.66-0.86)	
Age (year)				
15-29.9	1		1	
30-44.9	0.96 (0.91-1.00)	0.052	0.92 (0.85-0.99)	0.039
45-max	1.06 (1.00-1.12)	0.042	0.86 (0.79-0.93)	<0.001
WHO staging				
1	1		1	
2	0.92 (0.87-0.96)	<0.001	0.89 (0.84-0.95)	0.001
3	0.89 (0.84-0.94)	<0.001	0.90 (0.84-0.97)	0.004
4	0.87 (0.79-0.96)	0.005	1.04 (0.95-1.14)	0.392
BMI (kg/m²)				
Min-15.99				
16-16.99	0.91 (0.79-1.06)	0.268	0.96 (0.83-1.12)	0.628
17-17.99	0.76 (0.66-0.88)	<0.001	0.84 (0.73-0.97)	0.014
18-max	0.66 (0.59-0.74)	<0.001	0.68 (0.60-0.77)	<0.001

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 lost to follow-up for the two first years on ART in patients in option B+ (Haas AD, Lancet 2016; Tenthani L, AIDS 2014, Mutasa-ApolloT, PLoS One 2014).

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

- **Limitations:** deaths and lost 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 count 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 ≥ 500cells/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 when 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.