Determining the incidence of risk factors for the predictors/markers of cardio/coronary vascular disease (CVD), a non-communicable disease in an HIV sero-discordant population who received early or late Anti-retroviral therapy (ART).

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HPTN Regional Meeting

To determine the prevalence and incidence of NCDs in HIV population in the HPTN 052 Study

- Adverse Cardiovascular risks were uncommon overall ; with 64% of the study population aged 26-40 years.

- Dyslipidaemia was the most common adverse event accounting for close to 50% of the events.

- Adverse events such as dyslipidemia, diabetes and hypertension were increased in the delayed arm, this was not statistically significant.

- Females were 55% less likely to get AE complications as compared to the males.

- Early initiation of ART at a CD4+ cell count of 350-550 cells/mm3 may be beneficial in reducing cumulative risk of people living with HIV developing grade 2 or higher risk factors for CVD.

- Screening and expanded use of statins in routine care should be considered.

Appreciation

THANK YOU to the <u>HPTN Leadership</u> and <u>HPTN Scholar Program</u> for providing this platform to early career investigators, with all the necessary support and resources.

THANK YOU to all the <u>Mentors</u>, who take out of their time to provide guidance and mentorship. This experience would never be, if it wasn't because of the mentors.

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Its been a learning curve, a lot of learning from the first month of enrolment on the program, and the learning is continuing. Very exciting time in life of an upcoming researcher.

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Background/Rationale

- Globally the burden for Non-communicable diseases (NCDs) is 71% of 41 million annual deaths,

- In Sub-Saharan Africa (SSA) the burden of NCDs is large, growing and projected to overtake infectious diseases as major sources of morbidity and mortality by 2030*,

- HIV is a risk factor for development of cardio/coronary vascular disease (CVD), with a risk similar to smoking,

- Understanding risk factors for predictors/markers of CVD, among populations living with HIV is critical to mitigating it's onset.

*Ref: Guwatudde et al.

Background/Rationale

- Reprieve study a randomized controlled phase 3 large global study was conducted in multiple sites in people living with HIV.

- This study was designed to address the increased risk of heart disease experienced by PWH.

- The risk of heart disease is higher among people with HIV (PWH), including among younger individuals with lower predicted heart disease risk.

- The incidence of a major adverse cardiovascular event was 4.81 per 1000 person-years in the pitavastatin group and 7.32 per 1000 person-years in the placebo group (hazard ratio, 0.65; 95% confidence interval [CI], 0.48 to 0.90; P=0.002).

Background

- HPTN 052 was a randomized clinical trial of HIV sero-discordant couples with CD4 count 350-550 cells/ml^3 , comparing immediate versus delayed initiation of ART,
- This was a multisite study conducted in Brazil (Porto Alegre, Rio de Janeiro); India (Chennai and Pune); Malawi (Blantyre and Lilongwe); Thailand (Chiang Mai); Zimbabwe (Harare); and USA (Boston and Massachusetts),
- Results of the study showed that Early ART initiation:
  - decreased HIV acquisition in negative partners by 96%.
  - favored health outcomes for partners living with HIV,
- DSMB review meeting of the study in April 2011 recommended to stop delayed-ART initiation arm and start everyone on early-ART initiation.

Objectives

- To determine the **prevalence of predictors of CVD** (hypertension , diabetes, <mark>dyslipidemia</mark>, obesity, elevated liver enzymes, or renal disorders) measured as grade 2 or higher across the arms prior to DSMB recommendations.

- To determine the **incidence of predictors of CVD** (hypertension , diabetes, <mark>dyslipidemia</mark>, obesity, elevated liver enzymes, or renal disorders) across the arms post the DSMB recommendations.

Objectives

- To compare the incident risk factors for CVD across arms of early and late initiation of ART for the People living with HIV,

- To examine the association of age and sex with risk factors for CVDs,

- To estimate the cumulative incidence of event/predictors of CVD.

Methodology:-
Variables of interest were identified using case report forms (CRF) and defined as follows:

Variable	CRF Term.
Hypertension	Hypertension, Systolic hypertension, or Blood pressure increased.
Diabetes	Diabetes, Diabetes Mellitus, Hyperglycaemia, Type 2 Diabetes Mellitus, Diabetic Ketoacidosis, Diabetic vascular disorder, Blood glucose increased.
Dyslipidemia	Dyslipidaemia, Hypercholesterolaemia, Hypertriglyceridemia, Blood triglycerides increased, Low density lipoproteins increased, Blood cholesterol increased.
Liver disorder	Aspartate amino transferase increased, Alanine amino transferase increased, Hepatic enzyme increased, Transaminases Increased.
Renal disorder	Hypercreatinaemia, Blood creatinine increased.
Obesity	Obesity

Methods and Analysis Plan

- Prevalence: Events with DAIDS toxicity Table Grade ≥ 2 and pre-existing conditions prior to enrollment were quantified from the start of study to the DSMB recommendations.

- Incidence: Events with DAIDS toxicity Table Grade ≥ 2 post the DSMB recommendations date.

- To determine the Incidence: The following participants were excluded to determine incidence and cumulative incidence post DSMB recommendations.
    - Participants who did not have an ART start date
    - Participants who terminated prior to the DSMB date
    - Participants who had the conditions prior to the DSMB date (prevalent conditions)
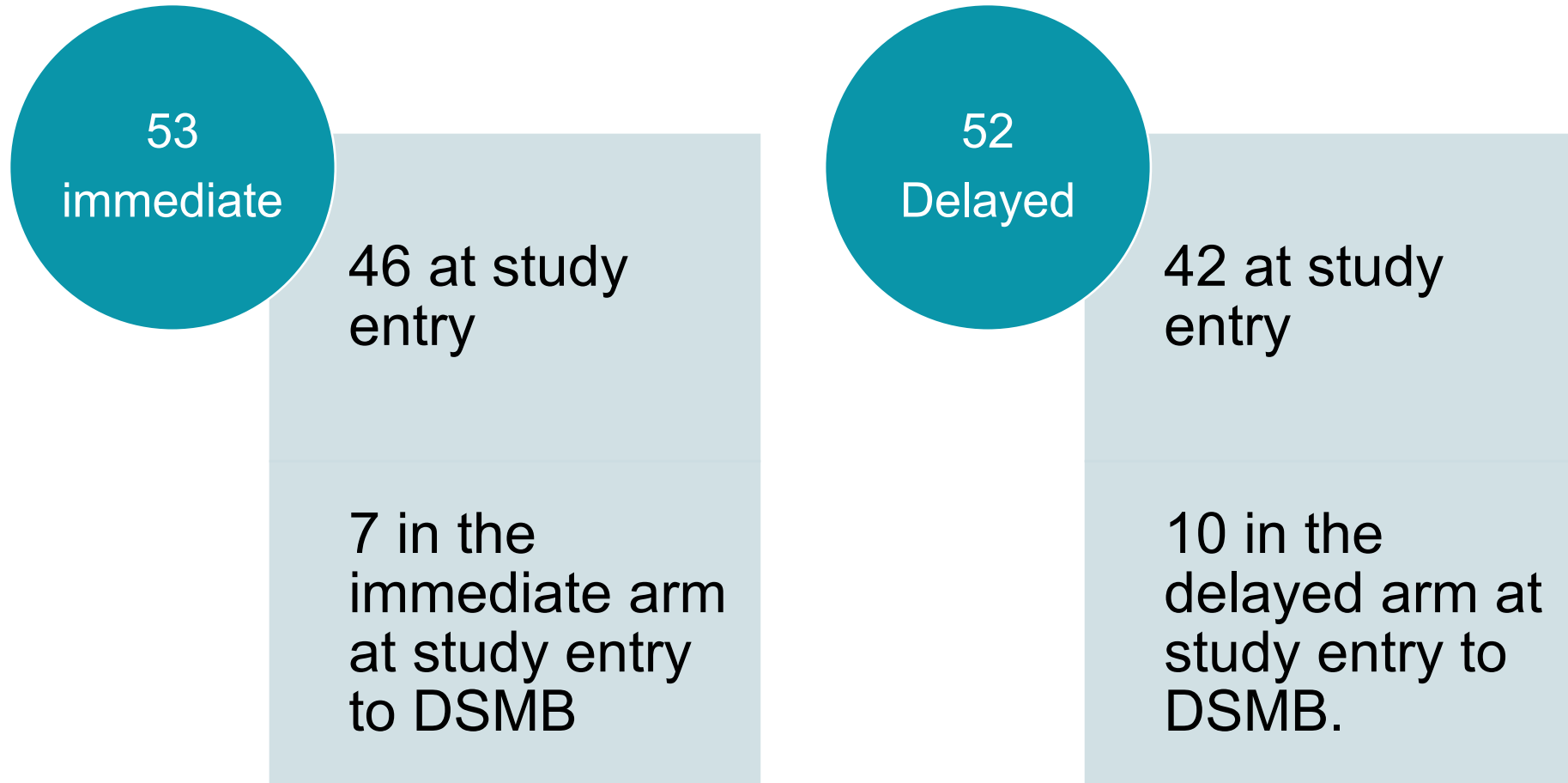
Analysis

- The association between Arm and the occurrence of NCD post-DSMB in participants who did not have a prevalent condition was evaluated by logistic regression, adjusting for sex.

- Event-free survival was estimated by the Kaplan-Meier method with a by-arm comparison using a log rank test.

- Time to first occurrence of an NCD event was defined as the time from the DSMB cutoff date to the first occurrence of an event, or the last visit for participants who did not have an event
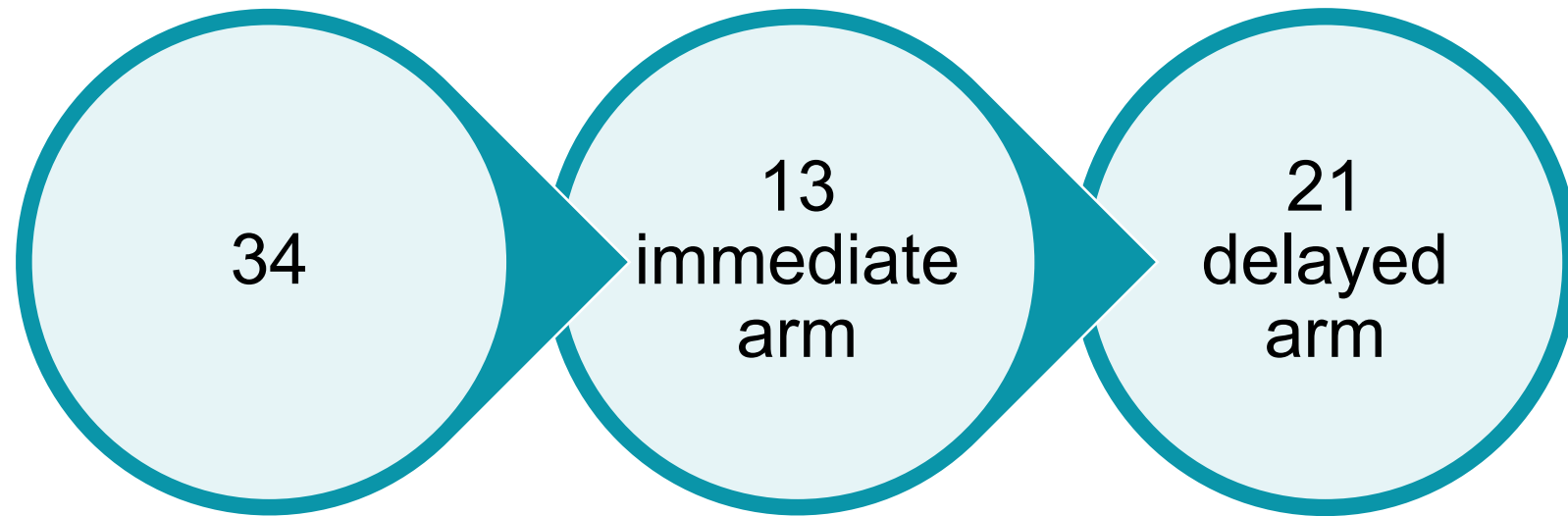
Demographics

| Variable	Total	Delayed arm	Immediate arm
Age Group			
18-25	252/1474 (17%)	129/706 (18%)	123/768 (16%)
26-40	939/1474 (64%)	449/706 (64%)	490/768 (64%)
41 and above	283/1474 (19%)	128/706 (18%)	155/768 (20%)
Sex			
Male	742/1474 (50%)	348/706 (49%)	394/768 (51%)
Female	732/1474 (50%)	358/706 (51%)	374/768 (49%)
Marital Status			
Single	77/1474 (5%)	36/706 (5%)	41/768 (5%)
Married	1154/1474 (78%)	550/706 (78%)	604/768 (79%)
Living with partner but not married	236/1474 (16%)	116/706 (16%)	120/768 (16%)
Separated or Divorced or Widowed	7/1474 (<1%)	4/706 (1%)	3/768 (<1%)

Prevalence

53 immediate

46 at study entry

7 in the immediate arm at study entry to DSMB

52 Delayed

42 at study entry

10 in the delayed arm at study entry to DSMB.

Incidence

Chi-square

	Immediate Arm	Delayed Arm
No Adverse event	755(98.3%)	685(97.0%)
Adverse event	13(1.7%)	21(3.0%)

Distribution of Adverse Events

Total AE Incidents by Arm
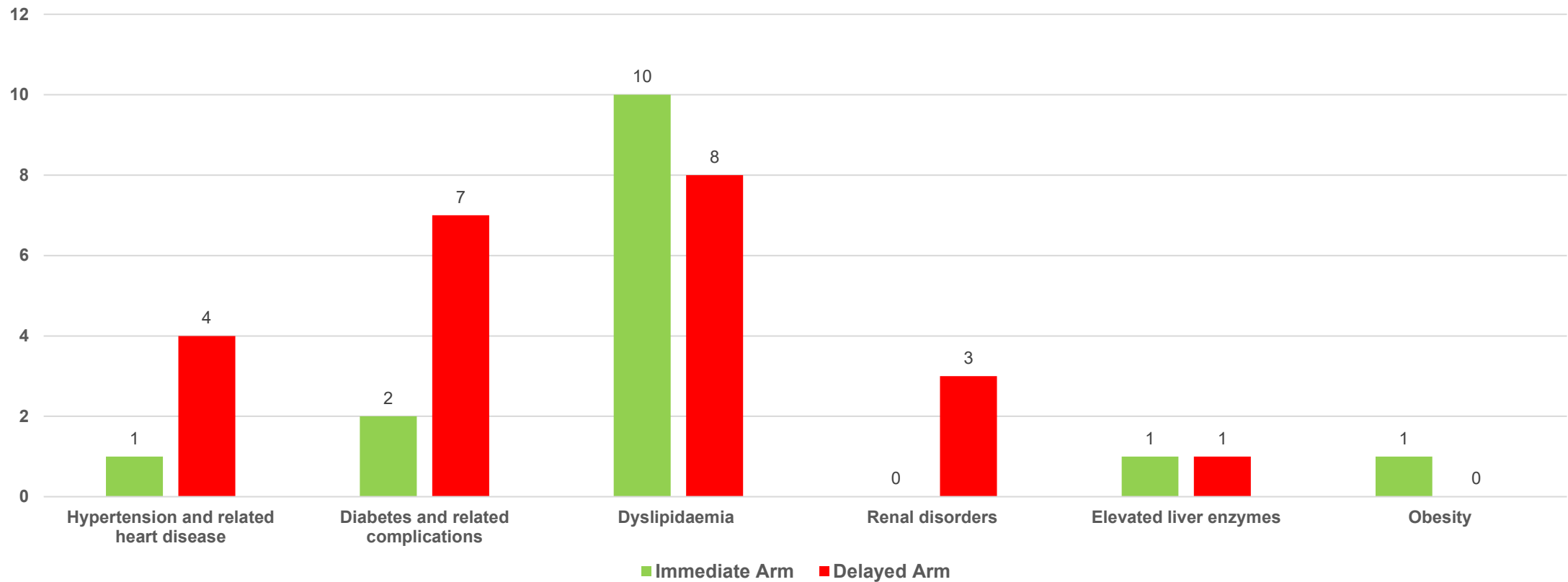
Probability of Developing Adverse Events
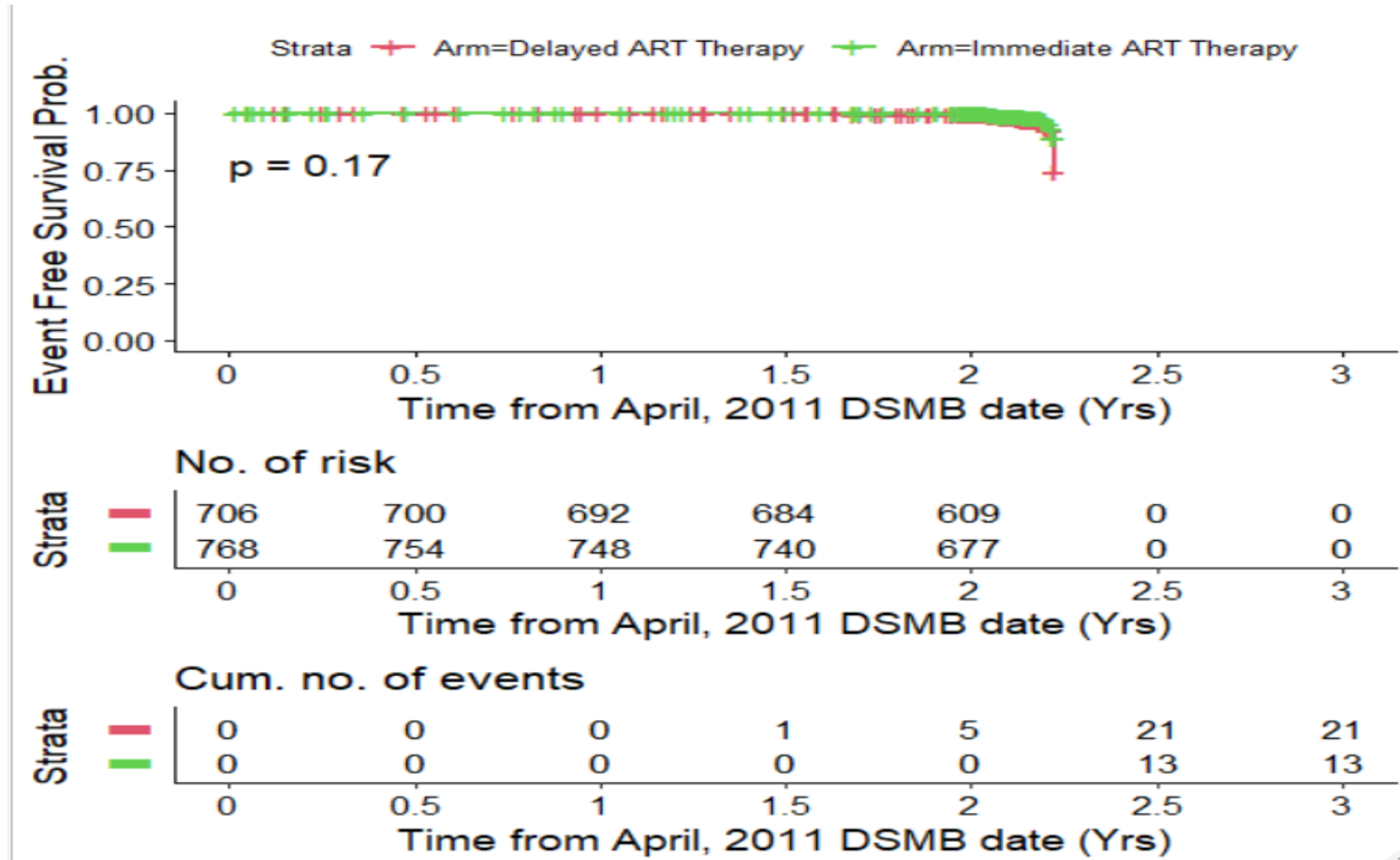
Results from multivariate analysis

Variable	Odds ratio	Lower 95%CI	Upper 95%CI	P value
Delayed ART Therapy versus Immediate ART Therapy.	1.85	0.92	3.73	0.09
Sex Female versus male	0.40	0.18	0.91	0.03
Age	1.02	0.98	1.06	0.28

- Early initiation of ART may be beneficial in reducing cumulative risk of people living with HIV developing grade 2 or higher risk factors for CVD.

- The prevalence and incidence of adverse events requiring intervention were low, however it is important to screen for these risk factors at HIV diagnosis so that clients can be advised on the benefits of initiating ART.

- PLWH taking ART should thus be offered screening for risk factors for cardiovascular diseases as routine care.

- Recent results from the REPRIEVE study highlight reduced cardiovascular risk in PLWH taking pitavastatin suggest expanded use of statins in routine care.

Thank you

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