Mortality Under Early Access to Antiretroviral Therapy Versus Eswatini's National Standard of Care: The MaxART Clustered Randomized Stepped Wedge Trial

Ariel Chao[1], Donna Spiegelman[1], Shaukat Khan[2], Fiona Walsh[3], Sikhatele Mazibuko[4], Munyaradzi Pasipamire[4], Boyang Chai[5], Ria Reis[6,7,8], Khudzie Mlambo[2], Wim Delva[9,10,11,12], Gavin Khumalo[13], Mandisa Zwane[14], Yvette Fleming[15], Emma Mafara[2], Anita Hettema[2], Charlotte Lejeune[2], Till Bärnighausen[16,17], Velephi Okello[18]

[1]Department of Biostatistics, Yale School of Public Health, New Haven, USA. [2]Clinton Health Access Initiative (CHAI), Mbabane, Swaziland/Eswatini. [3]Clinton Health Access Initiative (CHAI), Boston, USA. [4]Swaziland National ART program (SNAP), Ministry of Health, Mbabane, Swaziland. [5]Departments of Nutrition, Harvard T.H Chan School of Public Health, Boston, USA. [6]Leiden University Medical Center, Leiden University, Leiden, Netherlands. [7]Amsterdam Institute for Social Science, University of Amsterdam, Amsterdam, Netherlands. [8]Children's Institute, University of Cape Town, Cape Town, South Africa. Stellenbosch University, The South African Department of Science and Technology - National Research Foundation (DST-NRF) Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch, South Africa. [10]Hasselt University, Center for Statistics, Diepenbeek, Belgium. [11]Ghent University, International Centre for Reproductive Health, Gent, Belgium. [12]KU Leuven, Rega Institute for Medical Research, Leuven, Belgium. [13]Eswatini National Network of People Living with HIV (SWANNEPHA), Mbabane, Eswatini. [14] SAfAIDS, Manzini, Eswatini. [15]aidsfonds, Amsterdam, Netherlands. [16]Heidelberg Institute of Public Health, University of Heidelberg, Heidelberg, Germany. [17]Department of Global Health and Population, Harvard T.H Chan School of Public Health, Boston, USA. [18] Directorate Office, Ministry of Health, Mbabane, Eswatini.

Abstract

Introduction

- Current WHO guidelines recommend "treat all" HIV-infected individuals with ART
- MaxART: first Treat All implementation trial in government-managed health system
- Primary findings strongly supported scale-up of Treat All – this analysis examines mortality as an additional indicator of its impact

Methods

- Conducted in 14 Eswatinian health clinics with clinic-based stepped-wedge design
- All-cause, disease- and HIV-related mortality analyzed using Cox proportional hazard model

Results

- Treat All – no impact on all-cause (HR:1.12, 95% CI: 0.58-2.18, p=0.73), disease-related (HR:1.04, 95% CI: 0.52-2.11, p=0.90), and HIV-related mortality (HR: 0.93, 95% CI: 0.46-1.87, p=0.83)

Conclusion

- No immediate benefit of the Treat All strategy on mortality, nor evidence of harm.

Introduction

- Timing of ART initiation greatly influences survival outcomes among PLHIV[1,2,3].
- 2016: WHO recommended ART initiation in all adults with HIV, regardless of WHO clinical stage and CD4 count – "treat all" for immediate ART initiation following HIV diagnosis[4].
- MaxART: to determine the impact of Treat All on care retention and viral suppression versus standard of care (SoC)[5].
- Secondary analysis examines mortality associated with Treat All compared to later ART-initiation per SoC. Results on longevity will serve as additional indicator of impact.

Methods

- One random pair of clinics transitioned from Eswatini's SoC for ART initiation to Treat All every 4 months.
- All endpoints analyzed censoring SoC participants at clinic transition.
- Competing risks approach used to estimate disease-related and HIV-related mortality rates.

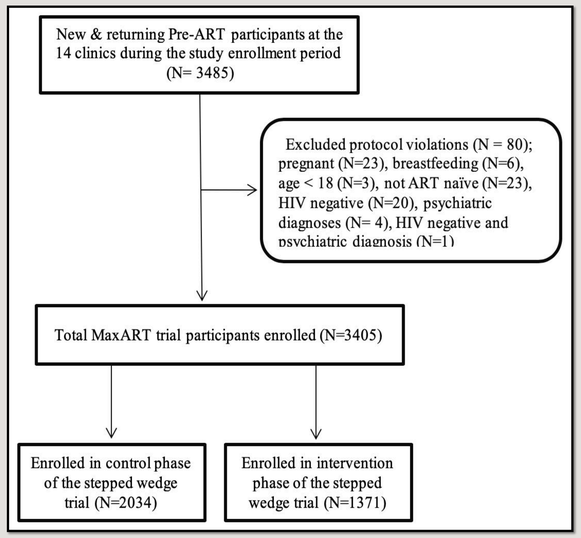

Figure 1: Flow diagram of participants enrolled

		Steps (4 month periods)									
Group	Clinic	1	2	3	*4	5	6	**7	8	9	Total
1	1	67	58	34	14	20	20	13	15	4	245
	2	81	27	23	10	8	18	13	13	7	200
2	3	27	13	17	6	14	12	13	12	8	122
	4	37	12	56	14	19	16	8	5	5	172
3	5	27	13	10	13	14	9	15	5	1	107
	6	50	27	33	34	25	23	17	11	6	226
4	7	20	5	6	10	4	8	4	5	14	76
	8	163	87	83	116	109	78	43	57	62	798
5	9	93	45	30	17	22	18	6	19	22	272
	10	64	28	29	29	18	35	15	16	7	241
6	11	59	23	30	34	30	27	24	21	10	258
	12	54	16	34	20	9	26	23	16	13	211
7	13	16	18	18	22	12	7	17	6	4	120
	14	112	63	36	27	34	33	24	10	18	357
	Total	870	435	439	366	338	330	235	211	181	3405

Figure 2: Clinic-based step-wedged trial diagram showing number of enrolled participants by clinic pair and steps

* Eswatini ART initiation guideline changed from a CD4 count threshold of ≤350 cells/μl to ≤500 cells/μl on December 1, 2016.

** Eswatini ART initiation guideline changed from a CD4 count threshold of ≤500 cells/μl to "treat all" on October 1, 2016.

Results

Endpoint	12-Month Mortality Rate (95% CI)		Hazard Ratio (95% CI)
	SoC	Treat All	
All-cause mortality	1.42% (0.66-2.17)	1.60% (0.78-2.40)	1.12 (0.58-2.18)
Disease-related mortality	1.18% (0.51-1.84)	1.36% (0.62-2.10)	1.12 (0.57-2.21)
HIV-related mortality	1.02% (0.40-1.64)	1.00% (0.40-1.59)	0.93 (0.46-1.87)

Table 1: 12-month mortality rates among SoC and Treat All participants, and multivariate-adjusted hazard ratio

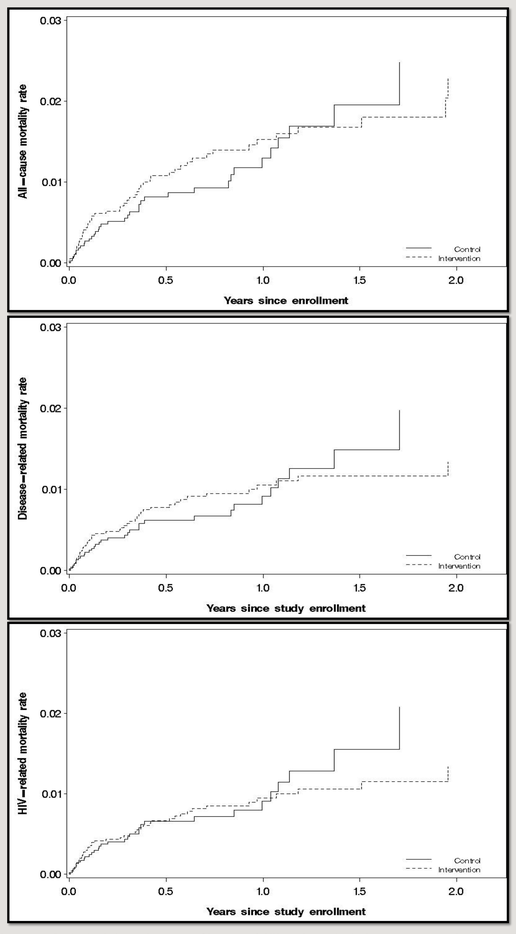

Figure 3: Multivariate-adjusted Kaplan-Meier curves by treatment group

Conclusion

- Primary analysis strongly supported scale-up of Treat All to improve retention and viral suppression rates, but mortality analysis inconclusive about impact on longevity among people living with HIV.
- Mortality under Treat All not significantly lower compared to SoC as hypothesized.
- However, since major purpose of Treat All is to decrease infectiousness so there are no new cases, also an important finding that there is no evidence of harm.
- Longer follow-up of participants necessary to establish long-term consequences, particularly mortality, of Treat All.

References

1. Farhan O, Achappa B, Bhaskaran U, et al. In-Patient Mortality among PLHIV: A 7-Year Hospital-Based Retrospective Study in Coastal South India. *Journal of the International Association of Providers of AIDS Care (JIAPAC)* 2017; 16(5): 494-498.
2. Zhao Y, Wu Z, McGoogan JM, et al. Immediate antiretroviral therapy decreases mortality among patients with high CD4 counts in China: a nationwide, retrospective cohort study. *Clinical Infectious Diseases* 2017; 66(5): 727-734
3. Ford N, Kranzer K, Hilderbrand K, 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): 2645-2650.
4. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. *World Health Organization*, 2016.
5. Walsh FJ, Barnighausen T, Delva W, et al. Impact of early initiation versus national standard of care of antiretroviral therapy in Swaziland's public sector health system: study protocol for a stepped-wedge randomized trial. *Trials* 2017; 18(1): 383.

MaxART For Better Health and Zero New HIV Infections

Ministry of Health Swaziland · Clinton Health Access Initiative · Stop AIDS Now! · SAfAIDS · SWANNEPHA · GNP+ · University of Amsterdam · SACEMA