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# Long-term survival among people living with HIV in rural South Africa: results from 6 years of observation in the ANRS 12249 ARTIC as prevention trial

K. Baisley<sup>1,2</sup>, J. Orne-Gliemann<sup>3</sup>, J. Larmarange<sup>4</sup>, M. Plazy<sup>3</sup>, D. Collier<sup>5,6</sup>, J. Dreyer<sup>1</sup>, T. Mngomezulu<sup>1</sup>, K. Herbst<sup>1,7</sup>, W. Hanekom<sup>1,5</sup>, F. Dabis<sup>4</sup>, M. Siedner<sup>1,8</sup>, C. Iwuji<sup>1,9</sup>

1. Africa Health Research Institute, Population Health, KwaZulu-Natal, South Africa, 2. London School of Hygiene and Tropical Medicine, Epidemiology and Population Health, London, United Kingdom, 3. University of Bordeaux, Inserm, Institut de Recherche pour le Développement (IRD), UMR1219, Bordeaux, France, 4. Centre Population et Développement (Ceped), Institut de Recherche pour le Développement (IRD), Université de Paris, Inserm, Paris, France, 5. Division of Infection and Immunity, University College London, London United Kingdom, 6. Cambridge Institute of Therapeutic Immunology & Infectious Disease, Cambridge, United Kingdom, 7. SAPRIN, South African Medical Research Council, KwaZulu-Natal, South Africa, 8. Harvard Medical School, Boston, Massachusetts, United States, 9. Brighton and Sussex Medical School, University of Sussex, Global Health & Infection, Brighton, United Kingdom.

## Introduction

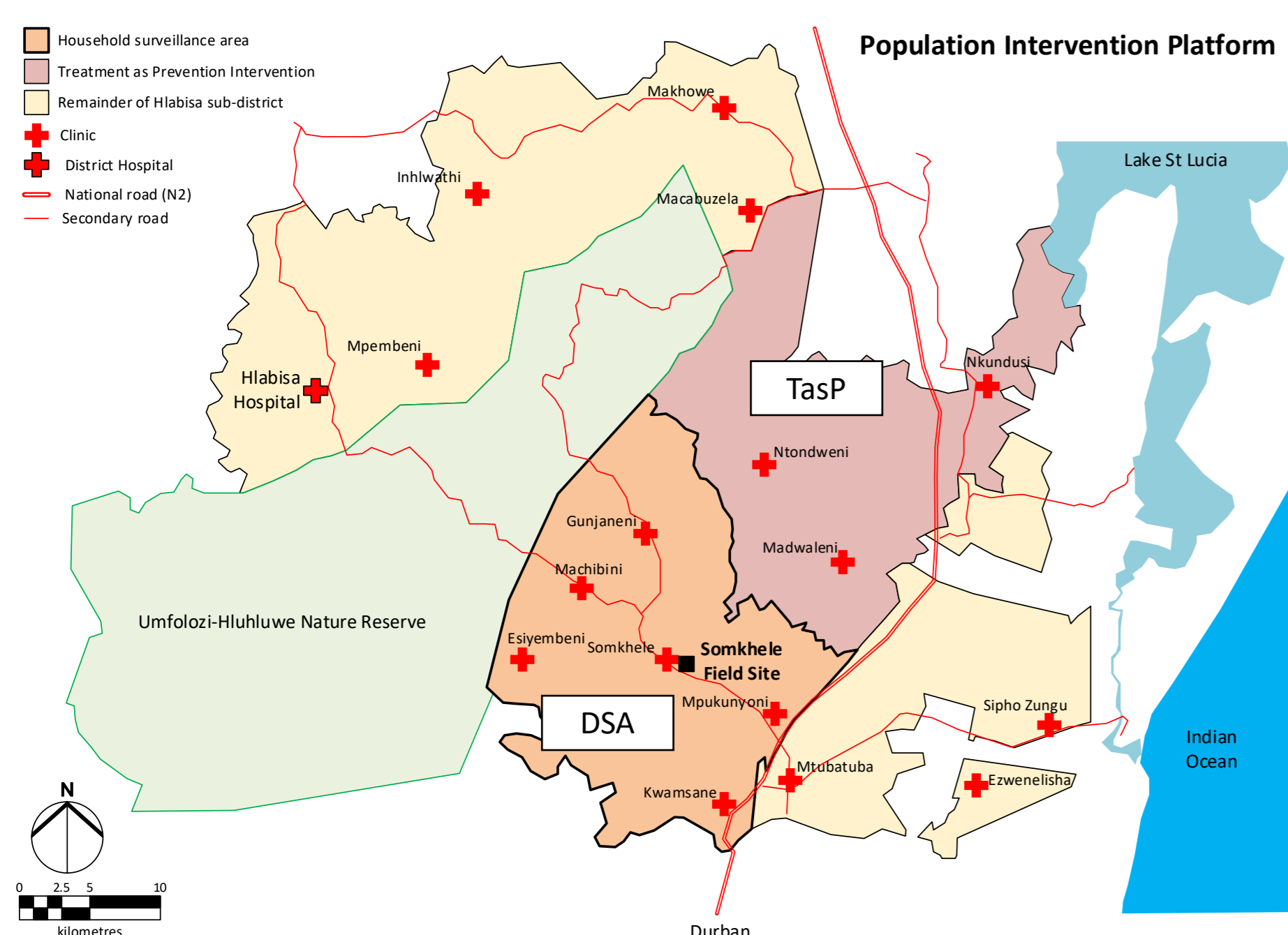
- South Africa has largest HIV epidemic in world, with 7.5 million people living with HIV (PLHIV)
- As of 2018, 22% of all deaths attributable to HIV
- Trials showed benefit of early antiretroviral therapy (ART) on mortality and morbidity; ART regardless of CD4 count is now global standard of care (1,2)
- Recent cluster randomised trials (CRT) of impact of immediate ART on HIV incidence have had conflicting effect on mortality (3,4)
- We aim to investigate whether a ‘treat-all’ policy in rural South Africa provided a long-term survival benefits

## Methods

### Study setting

- TasP CRT was implemented by Africa Health Research Institute (AHRI) in rural KwaZulu-Natal, South Africa from 2012 – 2016 (Fig 1)
- AHRI conducts annual household surveillance in demographic surveillance area (DSA) (Fig 1)
- TasP trial communities added to surveillance area in 2017

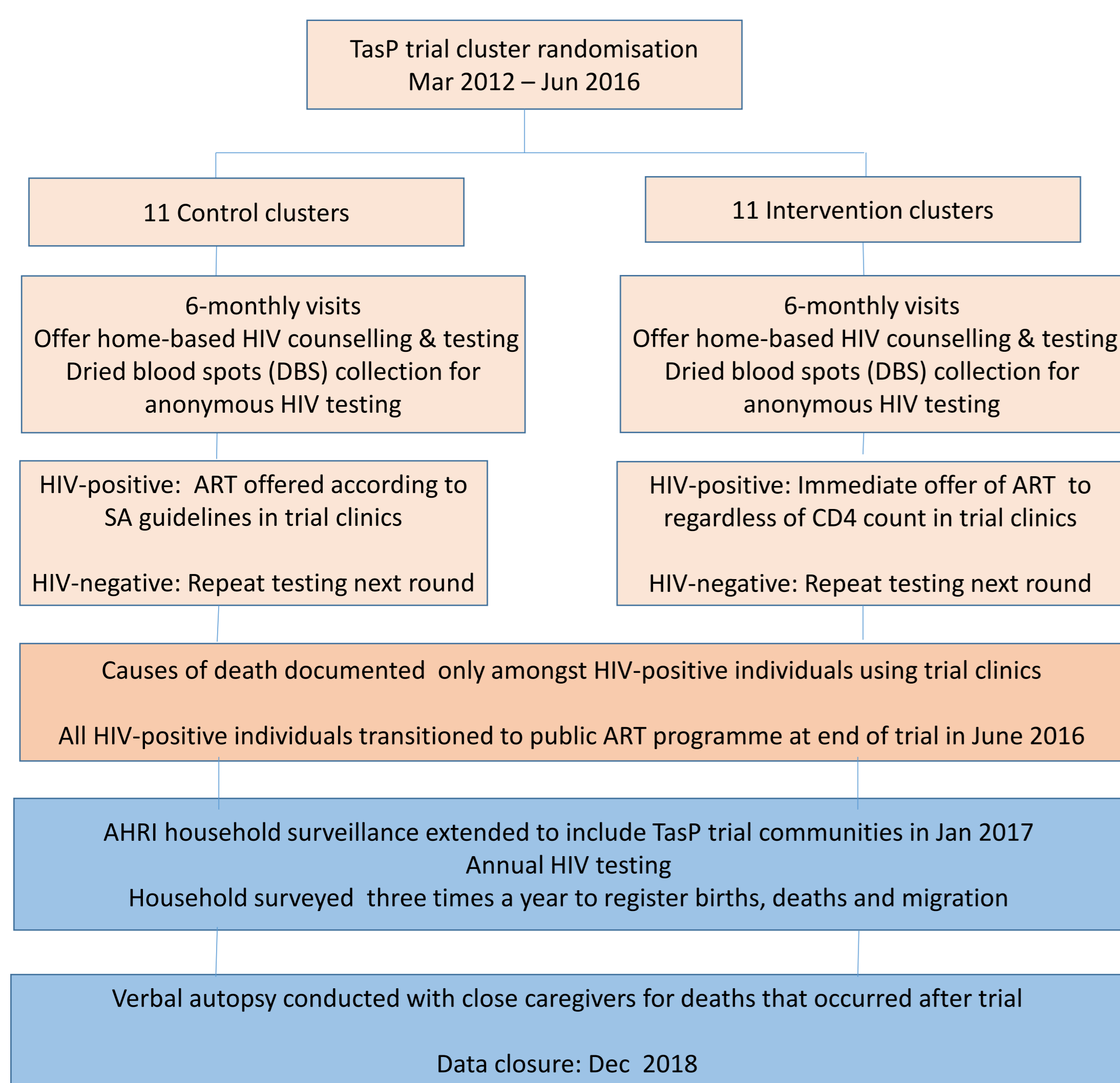
Figure 1. Location of former TasP communities and the AHRI DSA



### Study design

- In TasP CRT, ART was offered at trial clinics in each community (Figure 2)
- Participants already on ART could transfer to trial clinics if they preferred
- At end of trial, all participants on ART transferred to public ART programme
- Long term follow-up of TasP participants was possible through AHRI demographic surveillance

Figure 2. Study design and procedures



### Statistical analysis

- Data collected using REDCap and analysed using STATA 16.0
- Mortality in TasP trial examined among people identified as HIV positive (including diagnosed & aware of status PLUS undiagnosed but has positive DBS) to address question of whether offering immediate ART reduces mortality among all PLHIV
- Mortality also examined among PLHIV who were aware of their status and not on ART at time of diagnosis, and PLHIV who started ART at one of the trial clinics
- Rate ratios (RR) and 95% confidence intervals (CI) estimated for effect of trial arm on mortality using random effects Poisson regression to account for correlation within clusters
- Crude RRs adjusted for randomisation stratum only; adjusted (a)RRs adjusted for strata, age at trial entry, sex and period (during the trial, March 2012–June 2016; after trial end, July 2016–December 2018), to allow for temporal changes after end of trial
- Interaction term between period and treatment arm included, to allow effect of trial arm to differ between periods

## Results

### Participant characteristics

- Overall, 8555 individuals aged ≥16 years identified as HIV positive during trial; 87.4% (7474) aware of their status, including those newly diagnosed
- Among those aware of status, 5055 (67.6%) were not on ART
- Median (IQR) age of PLHIV was 32 (26-43) years, and 74.8% were women
- Among 1865 individuals who started or re-started ART at trial clinics, 1198 (64.2%) were ART-naïve at entry
- Mean CD4 counts at ART start were higher in intervention arm than control (451 vs 379, p<0.001)
- Mean CD4 higher in women than men (448 vs 342, p<0.001); 57.3% of men had CD4<350 at ART start, vs 39.6% of women (p<0.001)

### Mortality among all PLHIV

- 309 deaths among 8555 PLHIV recorded from 9 March 2012–31 December 2018
- Median (IQR) follow-up time was 3.79 (3.12-4.31) years; 6614 (77.3%) individuals seen in AHRI surveillance after trial end
- Crude mortality rate 9.3/1000 person-years in control arm vs 10.4/1000 person-years in intervention arm
- No evidence of effect of TasP intervention on all-cause mortality (aRR=1.10, 95% CI=0.85–1.43, p=0.46; Table 1)
- No evidence that effect of intervention differed between periods (p-value for treatment arm-period interaction=0.45)

Table 1. Mortality in all PLHIV in TasP trial

	Number individuals	Deaths /p-years	Rate/1000 p-years <sup>1</sup>	Crude RR (95% CI) <sup>1,2</sup>	Adjusted RR (95% CI) <sup>1,3</sup>
Arm				P=0.44	P=0.46
Control	4619	158 / 17,201	9.30	1	1
Intervention	3936	151 / 14,767	10.38	1.11 (0.86 -1.43)	1.10 (0.85 -1.43)
Period <sup>4</sup>				P<0.001	P<0.001
During trial	8555	205 / 17908	11.66	1	1
After trial	6621	104 / 14059	7.53	0.65 (0.51 -0.83)	0.66 (0.52 -0.84)
Stratum				P=0.55	P=0.60
1	1100	54 / 4809	11.39	1	1
2	3444	130 / 13,533	9.76	0.86 (0.59 -1.24)	0.84 (0.58 -1.21)
3	4011	125 / 13,625	9.27	0.81 (0.57 -1.17)	0.84 (0.58 -1.21)
Age at entry				P<0.001	P<0.001
<30 years	3432	74 / 12,649	5.92	1	1
30-49 years	3899	132 / 14,707	9.12	1.55 (1.17 -2.06)	1.41 (1.06 -1.88)
50+ years	1224	103 / 4611	22.63	3.86 (2.86 -5.21)	3.37 (2.49 -4.55)
Sex				P<0.001	P<0.001
Male	2155	144 / 7803	18.94	1	1
Female	6400	165 / 24,164	6.98	0.37 (0.29 -0.46)	0.40 (0.32 -0.50)

<sup>1</sup>Estimated from a Poisson regression model with random effects for community (cluster). <sup>2</sup>Adjusted for randomisation stratum. <sup>3</sup>Adjusted for all variables in table.

<sup>4</sup>During the trial March 2012-June 2016; after the trial July 2016-December 2018

### Mortality in PLHIV who were aware of their status

- 184 deaths among 5055 PLHIV who were aware of their status and not on ART at time of diagnosis
- No evidence of an effect of TasP intervention on mortality (aRR=1.16, 95%CI=0.81-1.67, p=0.42; Table 2), or that effect differed between periods (p-value for interaction=0.97)

Table 2. Mortality among PLHIV in TasP trial who were aware of their status and not on ART at the time of diagnosis

	Number individuals	Deaths /p-years	Rate/1000 p-years	Crude RR (95% CI)	Adjusted RR (95% CI)
Arm				P=0.40	P=0.42
Control	2686	92 / 9526	9.64	1	1
Intervention	2369	92 / 8441	11.24	1.17 (0.81 -1.70)	1.16 (0.81 -1.67)
Period				P=0.12	P=0.16
During trial	5055	108 / 9531	11.55	1	1
After trial	3974	76 / 8436	9.15	0.79 (0.59 -1.07)	0.81 (0.60 -1.09)
Stratum				P=0.84	P=0.93
1	573	22 / 2337	9.72	1	1
2	2077	83 / 7704	11.17	1.15 (0.65 -2.04)	1.06 (0.60 -1.85)
3	2405	79 / 7927	10.05	1.03 (0.59 -1.80)	0.98 (0.56 -1.70)
Age at entry				P<0.001	P<0.001
<30 years	2259	48 / 7923	6.09	1	1
30-49 years	2174	78 / 7859	10.04	1.65 (1.15 -2.37)	1.50 (1.04 -2.15)
50+ years	622	58 / 2185	26.53	4.37 (2.98 -6.42)	3.86 (2.62 -5.68)
Sex				P<0.001	P<0.001
Male	1323	87 / 4593	19.36	1	1
Female	3732	97 / 13,374	7.40	0.38 (0.29 -0.51)	0.42 (0.31 -0.56)

### Mortality among PLHIV who started or restarted ART at one of the trial clinics

- 1865 individuals started or restarted ART at a trial clinic, median (IQR) follow-up time on ART was 3.43 (2.78-4.21) years
- Mortality lower in intervention arm than control (11.7/1000 vs 17.1/1000 person-years)
- Suggestion of benefit of the intervention on mortality overall (aRR=0.69, 95%CI=0.45-1.04, p=0.08; Table 3).
- Intervention effect differed between periods (p for interaction=0.05), with decreased mortality in intervention arm during trial (aRR=0.49, 95%CI=0.28-0.85, p=0.01), but not after trial end (aRR=1.15, 95%CI=0.59-2.21, p=0.69)

Table 3. Mortality among PLHIV in TasP trial who started ART at one of the trial clinics and were not on ART at time of entry

	Number individuals	Deaths /p-years	Rate/1000 p-years	Crude RR (95% CI)	Adjusted RR (95% CI)
Arm				P=0.07	P=0.08
Control	912	52 / 3044	17.09	1	1
Intervention	953	39 / 3341	11.67	0.69 (0.45 -1.04)	0.69 (0.45 -1.04)
Period				P=0.16	P=0.20
During trial	1865	55 / 3380	16.27	1	1
After trial	1400	36 / 3005	11.98	0.73 (0.48 -1.13)	0.75 (0.49 -1.16)
Stratum				P=0.71	P=0.79
1	224	11 / 884	12.45	1	1
2	917	50 / 3236	15.45	1.24 (0.65 -2.38)	1.12 (0.58 -2.16)
3	724	30 / 2265	13.24	1.06 (0.53 -2.12)	0.96 (0.47 -1.95)
Age at entry				P<0.001	P<0.001
<30 years	650	17 / 2179	7.80	1	1
30-49 years	886	41 / 3091	13.26	1.71 (0.97 -3.01)	1.43 (0.81 -2.54)
50+ years	329	33 / 1114	29.61	3.85 (2.14 -6.92)	3.16 (1.75 -5.73)
Sex				P<0.001	P<0.001
Male	534	45 / 1789	25.15	1	1
Female	1331	46 / 4596	10.01	0.40 (0.26 -0.60)	0.44 (0.29 -0.67)

## Discussion

- Amongst PLHIV who started ART during the TasP trial, immediate ART decreased mortality considerably during the trial; however, that benefit was no longer evident after the trial ended
- No evidence that offering immediate ART reduced mortality among all PLHIV over 6 years of follow-up, or amongst those aware of their HIV status but not on ART; this can be explained by suboptimal linkage to care during the TasP trial (5)
- To achieve maximum benefit of immediate ART, barriers to ART uptake and retention in care need to be addressed