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

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Introduction

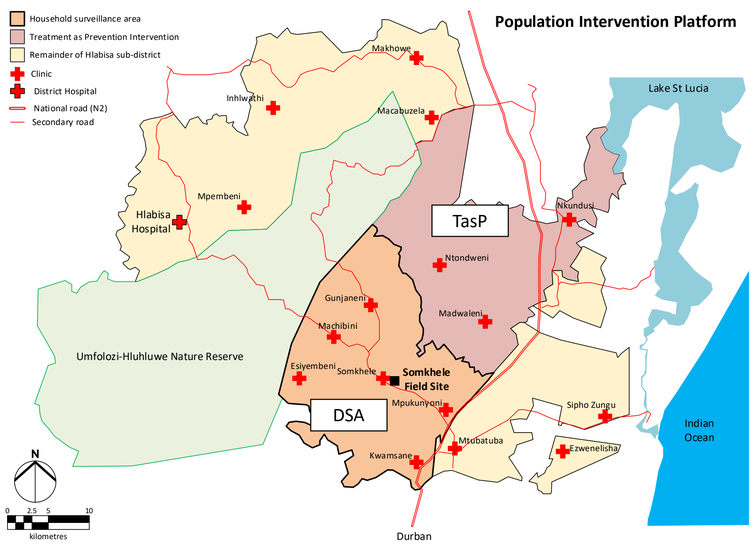
- South Africa has largest HIV epidemic in world, with 7.5 million people living with HIV (PLHIV)
- As of 2018, 22% of all deaths attributable to HIV
- Trials showed benefit of early antiretroviral therapy (ART) on mortality and morbidity; ART regardless of CD4 count is now global standard of care (1,2)
- 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

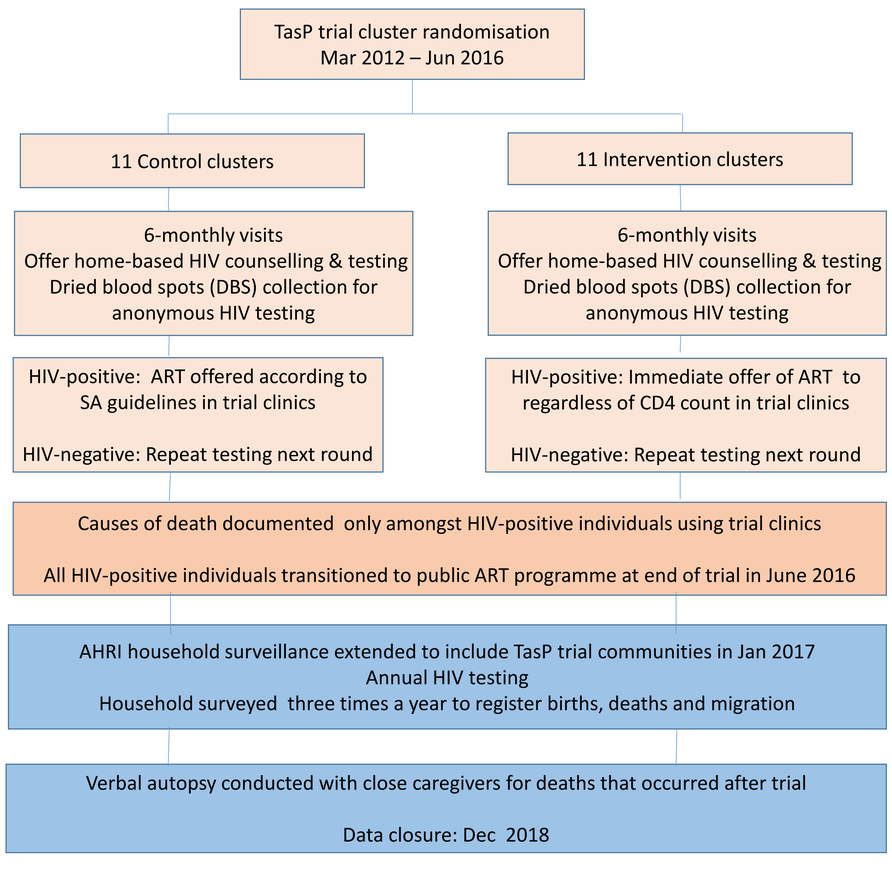
Figure 1. Location of former TasP communities and the AHRI DSA



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[1]	Crude RR (95% CI)[1,2]	Adjusted RR (95% CI)[1,3]
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[4]				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)

[1]Estimated from a Poisson regression model with random effects for community (cluster). [2]Adjusted for randomisation stratum. [3]Adjusted for all variables in table. [4]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

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