The impact of the South African antiretroviral treatment programme on the age-standardised incidence rate of Kaposi sarcoma, 1999–2016: An interrupted time series analysis

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ABSTRACT

Objective: The objective of this study was to quantify the impact of the South African antiretroviral treatment programme on the age-standardised incidence rate of Kaposi sarcoma among black South African residents of all ages.
Methods: We performed an interrupted time series analysis using routinely collected, histologically confirmed surveillance data from the South African National Cancer Registry for the years 1999 to 2016. The analysis was performed using R statistical software. The total number of cases was 29,623 (12,475 females and 17,166 males). The background antiretroviral treatment coverage was less than 1% at the time that the antiretroviral programme was introduced and increased to over 50% in 2016.
Results: In 1999, the age-standardised rates were 1.48 and 2.82 cases per 100,000 per year for black females and males, respectively. These rates increased to 5.52 and 7.46 in 2008 before declining. The antiretroviral treatment programme was started in 2004. Five years after 2008 (nine years after the antiretroviral programme was introduced), the predicted standardised rates were 58.3% and 50.3% lower for females and males, respectively, than what they would have been without the treatment programme.
Conclusion: Introduction of the antiretroviral treatment programme was associated with a decrease of over 50% in the predicted age-standardised incidence rates of Kaposi sarcoma.
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Introduction

The human immunodeficiency virus (HIV) epidemic is a source of HIV-related morbidity and mortality around the world. According to UNAIDS (2020), in 2018, there were an estimated 37.9 million individuals living with HIV worldwide, with 20.6 million from eastern and southern Africa, including 7.7 million in South Africa (SA).

Kaposi sarcoma (KS), caused by the Kaposi sarcoma herpesvirus (KSHV), is the most frequently diagnosed malignancy in HIV-infected patients in sub-Saharan Africa (Cattelan et al., 2001). The risk of KS is substantially increased by immunodeficiency induced by HIV infection (Guiguet et al., 2009; Engels et al., 2008). In most parts of the world, KS is a rare type of cancer, but in some areas in sub-Saharan Africa, it is now, in the era of the HIV epidemic, one of the most common cancers, mostly occurring in people infected with HIV, with more than 90% of known cases being HIV sero-positive (Sengayi et al., 2017). Ferlay et al. (2015) have drawn attention to the fact that the incidence rate of KS in SA has increased dramatically since the onset of the HIV epidemic. These rates have increased from age-standardised incidence rates (ASRs) of less than 3 per 100,000 per year (1999) to ASRs as high as 7.7 (2008) among black (those considered to be wholly of African descent) South African males, with cases reported in all age groups (South African National Cancer Registry, last accessed in May 2020).

Following the introduction of antiretroviral therapy (ART) for HIV infected people, the incidence rate of KS has decreased in North America, Europe and Africa (Franceschi et al., 2010; Rubinstein et al., 2014; Sitas et al., 2008; Chaabna et al., 2013). While the risk of KS has been noted to be increased by between

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1000 and 5000 times among people who are HIV sero-positive in Europe and the USA, in Africa, where KS has been endemic for many decades before the HIV epidemic, the risk among those with HIV is of the order 30–50 times higher than in people without HIV infection (Sitas et al., 2008). In Africa, a decrease of ASRs from 32/100,000 to 4.9/100,000 was noted and ascribed to ART between 1992 and 1999 (International Collaboration on HIV and Cancer, 2000). The South African government introduced the national ART programme in 2004 (South African Department of Health, 2004). By 2018, ART coverage in SA was approximately 62.3% of those living with HIV (UNAIDS, 2018). The South African treatment guidelines for ART have changed over time (South African Department of Health, 2004; South African Department of Health, 2013).

In the initial 2004 guidelines, ART was offered to people who had CD4+ cell counts of less than 200 cells/μL or who had WHO clinical stage III or IV disease. Stage IV disease included patients with a diagnosis of KS. For patients with counts between 200 and 350, treatment could commence on an individual basis depending on the clinical signs and symptoms. For counts above 350 cells, treatment was to be deferred. In the revised guidelines released in 2013, the recommendation was to initiate treatment with ART for all people living with HIV who had CD4+ counts less than 350 cells/μL or who had WHO clinical stages III or IV disease (WHO, 2013). Children under the age of 5 years were also then automatically eligible for treatment, irrespective of the CD4+ cell count, as were pregnant women or women who were breastfeeding.

In their hospital-based study, Sengayi et al. (2017) showed that 357 out of 370 KS patients (96.5%) were HIV sero-positive between 2004 and 2012. The presentation of HIV-related KS usually occurs at CD4+ cell counts of below 350 cells/μL. A study of 33 cases of HIV-related KS in Kenya, for example, showed that 26/33 had CD4+ counts below 300 at presentation (Lupia et al., 2017). In addition, 25/33 had WHO stage 3 or stage 4 disease at the time of presentation. Furthermore, it is noteworthy that, in South Africa, patients with HIV infection usually present relatively late in the course of their disease (Fomundam et al., 2018). In the report by Fomundam et al. (2018), based on data from several different sites, there were 12,413 patients who were newly diagnosed as HIV positive. Of these, 66% had CD4+ counts available at the time of diagnosis. On the basis of these results, at presentation, 33% had CD4+ counts ≤200 (or WHO stage IV), and 27% had counts between 201 and 350 (or WHO stage III).

South African patients with KS are predominantly from the black population, with up to 98.9% reported to be black South Africans in the study reported by Sengayi et al. (2017), and 90.91% being black South Africans in a community-based study that included cases that were not submitted for histological confirmation (South African National Cancer Registry, 2018).

These two studies also cast light on the proportion of known cases that is histologically proven. In the hospital-based study, 99.4% of the KS cases were histologically proven in 2004–2008, and 99.5% were histologically proven in 2009–2012. In the community-based study, 70/79 (93.5%) were morphologically verified.

The International Association for Research in Cancer (IARC) has estimated, by modelling with the use of data from the death notification system, laboratory submitted data to the NCR and a community based regional cancer registry, as well as data from neighbouring countries, that there were 2260 cases of KS in South Africa in 2018 (International Agency for Research on Cancer, 2018). The most recent number of KS cases that is available for comparison is for 2016 when the total number of KS cases reported from the country's laboratories (both sexes and all population groups combined) was 1831 cases (South African National Cancer Registry, accessed 2020).

Table 1
The world standard population

Age class index	Age class	Population
1	0–4	12,000
2	5–9	10,000
3	10–14	9000
4	15–19	9000
5	20–24	8000
6	25–29	8000
7	30–34	6000
8	35–39	6000
9	40–44	6000
10	45–49	6000
11	50–54	5000
12	55–59	4000
13	60–64	4000
14	65–69	3000
15	70–74	2000
16	75–79	1000
17	80–84	500
18	85+	500
Total population	100,000	

Source: Jensen et al. (1991).

To our knowledge, although previous published studies in Africa have compared the incidence rate of KS prior to the introduction of ART to the incidence rate at some time after ART was made available, this is the first report of the impact of ART on the incidence of KS using interrupted time series analysis (ITSA).

The advantage of using ITSA is that it compares the actual reported case numbers to what they would have possibly been if the intervention (ART) had not occurred. A simple pre- and post-intervention comparison would underestimate the benefits of the intervention if the incidence rate was increasing at the time of the intervention and over-estimate the benefits if the incidence rate was declining at the time of the intervention.

Regarding HIV-related KS incidence and the ART intervention, the incidence of KS was increasing in South Africa at the time of the intervention. Hence, the use of ITSA prevents the underestimation of the impact of ART on KS incidence. This type of analysis is therefore relevant if one wishes to estimate the real impact of ART, both for economic analyses as well as for advocacy purposes.

Using the South African data for black South Africans, this study intended to estimate the impact on the incidence at five years after the ASRs started to fall (nine years after the introduction of the ART programme), given the prevailing historical extent of ART coverage, using ITSA. Despite SA having one of the highest burdens of HIV/AIDS and KS across the world, to our knowledge, the impact of the South African national ART treatment programme on KS has not yet been quantified using ITSA, which has prevented a more realistic estimation of the impact of ART on KS incidence.

Methods

Data sources

The population at risk for this analysis consisted of the total population of black South African residents, both those with HIV infection and those without. All ages were considered to be at risk as HIV-related KS has been reported in all 5-year age groups used for the estimation of the ASRs. Similarly, with regards to the numerators, all reported cases among South African residents were included irrespective of the patient's age or HIV sero-status. This study makes use of data available from the South African National Cancer Registry (NCR) for black South African residents, of all ages, with KS. These laboratory-sourced data do not include information about HIV sero-status, and thus we have estimated the impact on

KS incidence regardless of HIV sero-status. The NCR reports ASRs each year for four resident population groups, the largest of which is for black South African residents. For the years included in this study, the NCR analysed and reported only laboratory-confirmed cases of cancer. Figure 2 illustrates the burden of HIV and the estimated proportion of all South African residents (all population groups combined) living with HIV and receiving ART over the period of this study. The ART coverage for just the black population is not available for SA. The HIV burden data were obtained from Statistics South Africa's website (Statistics South Africa, accessed in June 2020) which presents the HIV burden as the number of cases among those aged 15–49 divided by the total population.

Inclusion criteria

We measured the impact of the ART programme on the incidence of KS cases recorded by the cancer registry, and we have confined our analysis to cases of KS reported among black South African residents. While blacks account for more than 80% of South Africa's population, (Statistics South Africa, last accessed June 2020), it has been established that, prior to the introduction of the national ART programme in 2004, the ART coverage was approximately 1% (Johnson et al., 2017). The reason for focusing on the black population group is that it is the largest population group accessing healthcare in the public sector of SA. ART was widely available through private funding for South Africans prior to 2004 but was largely inaccessible to members of the black population because the majority of them did not have medical insurance at the time. Therefore, the impact of the ART treatment programme in the private sector and thus non-black populations would already have been felt prior to the introduction of the national ART programme. It made sense for us, therefore, to study trends of KS among the black population when measuring the impact of the national public sector ART programme on the incidence of KS.

Data analysis

In this study, an ITSA was used to analyse data submitted to the NCR of South Africa, for black residents of the country, through routine reporting of all laboratory-confirmed cases of KS for the years 1999–2016. Private and public sector laboratories submit these data to the NCR routinely. Furthermore, we chose to measure the impact of the programme on the ASRs of KS, rather than on the number of cases, as the population structure of South Africa has changed over the 16-year study period. The National Cancer
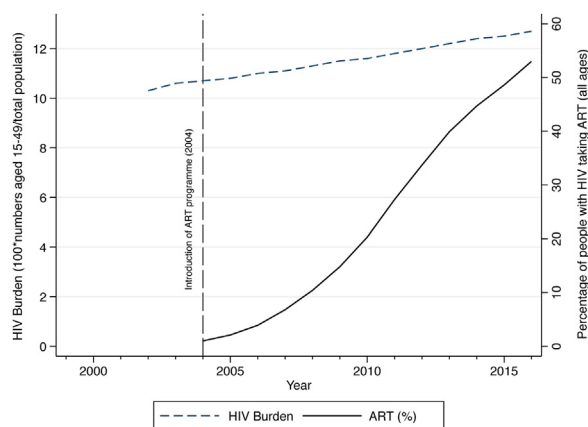
Figure 2. The South African HIV burden and proportion of people with HIV who are taking ART by year (all population groups). Sources of raw data: Statistics South Africa (accessed June 2020); and Johnson et al. (2017).

Registry excludes any tumours that were diagnosed in non-residents of South Africa. Duplicate submissions for the same tumour in the same individual are also excluded through a formal process of deduplication. The database of tumours submitted, names and identification data, including date of birth, full names and national identification number, is maintained by the registry and dates back to 1986. If a person is reported to have a second or subsequent tumour of the same kind but at a different site, then only the first occurrence is retained. Removal of duplicates is performed using probabilistic record linkage methods and SAS statistical software.

The South African NCR uses hot-deck imputation to allocate the population group in those cases where the population group has not been recorded by the reporting laboratory. Cases with missing information about population group are matched using recorded sex, names and surnames. From the date of the tumour report, the database of all previously submitted cases, dating back to 1986, is searched backwards sequentially in time, until a previous report (any tumour) is received for a person with the same sex, name and surname and who has a known population group recorded. That population group is then assigned for the individual with the missing population group information.

For missing data on sex, age and population group (the hot-deck method does not always succeed in allocating a population group), the pro-rata method of allocation of the tumours was used, as is recommended by IARC (Jensen et al., 1991). In this method, the distribution of tumours, with known demographic details, between different population group, sex and age group categories, is used to calculate the probability of a particular tumour falling within a particular population group/sex/age-group sub-population. These probabilities are then used to apportion each case with one or more missing piece of demographic information.

For example, if a particular record is known to be for a black person aged between 45 and 49 years but the sex of the patient is not recorded and if the tumour cases in this population group and age group are known to be comprised of 40% male and 60% female sexes, then this tumour will be allocated 0.4 to male and 0.6 to female. First, missing population group information is allocated. Thereafter, missing information about sex is allocated. Thereafter, cases are dealt with in a similar way where two variables are missing, and, finally, missing five-year age groups are allocated.

Direct standardisation was used to calculate the ASRs. The World Standard Population used was as recommended by IARC (Jensen et al., 1991). The standard population is the same for males and females and is shown in Table 1; there are 18 age categories.
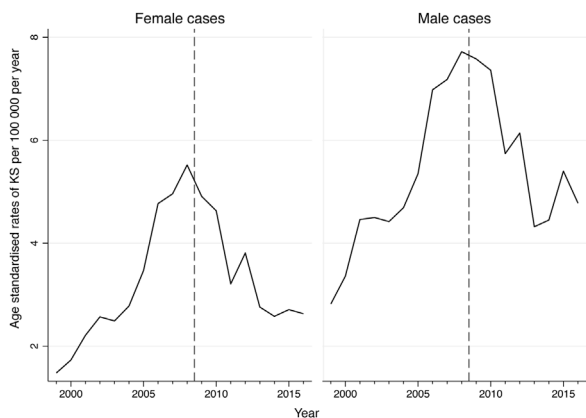
Figure 1. Time series graph for KS ASR vs. year, by sex, for black South Africans: 1999–2016. Source of data: South African National Cancer Registry, last accessed May 2020.

Table 2
Incidence rates per 100,000 per year by year and sex.

Females						Males					
Year	Cases	Population	Crude rate	ASR	95% CI	Year	Cases	Population	Crude rate	ASR	95% CI
1999	269	17,786,998	1.51	1.48	1.30–1.66	1999	427	16,639,605	2.57	2.82	2.54–3.11
2000	314	18,123,902	1.73	1.73	1.53–1.93	2000	503	16,946,862	2.97	3.36	3.05–3.68
2001	416	18,442,577	2.26	2.21	1.99–2.43	2001	700	17,240,861	4.06	4.46	4.11–4.81
2002	493	18,729,861	2.63	2.57	2.34–2.8	2002	723	17,506,462	4.13	4.50	4.15–4.85
2003	488	18,983,646	2.57	2.49	2.26–2.72	2003	728	17,741,216	4.10	4.42	4.08–4.75
2004	533	19,204,754	2.78	2.78	2.53–3.02	2004	767	17,946,938	4.27	4.69	4.34–5.04
2005	708	19,399,334	3.65	3.47	3.21–3.73	2005	877	18,130,349	4.84	5.35	4.97–5.72
2006	920	19,104,400	4.82	4.77	4.45–5.09	2006	1139	18,558,500	6.14	6.98	6.56–7.41
2007	1021	19,304,300	5.29	4.96	4.65–5.27	2007	1267	18,775,600	6.75	7.18	6.76–7.59
2008	1153	20,037,100	5.75	5.52	5.19–5.84	2008	1382	18,528,000	7.46	7.72	7.30–8.15
2009	1057	20,235,200	5.22	4.91	4.61–5.21	2009	1364	18,901,000	7.22	7.58	7.15–8.00
2010	1005	20,368,100	4.93	4.63	4.33–4.92	2010	1342	19,314,500	6.95	7.36	6.94–7.78
2011	687	20,734,237	3.31	3.21	2.96–3.46	2011	959	19,472,038	4.92	5.74	5.35–6.13
2012	819	21,454,437	3.82	3.81	3.54–4.07	2012	1104	20,484,361	5.39	6.14	5.76–6.53
2013	653	21,676,300	3.01	2.76	2.54–2.97	2013	888	20,607,800	4.31	4.32	4.01–4.62
2014	612	22,165,000	2.76	2.58	2.37–2.79	2014	902	21,168,700	4.26	4.45	4.14–4.76
2015	654	22,574,500	2.89	2.71	2.50–2.93	2015	1090	21,653,500	5.06	5.40	5.05–5.77
2016	655	22,990,700	2.84	2.63	2.42–2.84	2016	1004	22,119,200	4.57	4.78	4.46–5.12

ASR = age-standardised rate; CI = confidence interval. Source: www.nicd.ac.za/centres/national-cancer-registry; and http://www.statssa.gov.za/?page_id=1859. For the mid-year population estimates for years 1999–2006, the mid-year population estimates were provided by the Centre for Actuarial Research, South African Medical Research Council and the Actuarial Society of South Africa.

Table 3
Model parameter estimates for female cases: three models compared.

	Coefficient	95% confidence interval	p-value
Ordinary least squares model			
Intercept	0.71	0.08 to 1.33	0.030
Time	0.45	0.35 to 0.55	<0.001
Level	−0.31	−1.20 to 0.59	0.478
Trend	−0.79	−0.97 to −0.62	<0.001
Autoregressive model [AR(5)]			
Intercept	0.51	0.26 to 0.75	0.001
Time	0.48	0.43 to 0.52	<0.001
Level	−0.16	−0.64 to 0.32	0.527
Trend	−0.86	−0.93 to −0.79	<0.001
Model with trend-squared			
Intercept	0.71	0.18 to 1.23	0.020
Time	0.45	0.37 to 0.54	<0.001
Level	0.58	−0.58 to 1.74	0.346
Trend	−1.32	−1.87 to −0.77	<0.001
Trend-squared	0.06	0.00 to 0.12	0.073

Year coefficient is the slope of the pre-intervention regression line; level coefficient = the predicted fall in the ASR immediately after the ARV programme was introduced; trend coefficient = the net change in the slope from before to after the intervention.

Table 4
Model parameter estimates for male cases: two models compared.

	Coefficient	95% confidence interval	p-value
Ordinary least squares model			
Intercept	2.27	1.36 to 3.18	<0.001
Time	0.52	0.38 to 0.67	<0.001
Level	0.1	−1.20 to 1.40	0.871
Trend	−0.94	−1.19 to −0.69	<0.001
Model with trend-squared			
Intercept	2.27	1.55 to 3.00	<0.001
Time	0.52	0.41 to 0.64	<0.001
Level	1.57	−0.04 to 3.17	0.078
Trend	−1.82	−2.58 to −1.06	<0.001
Trend-squared	0.10	0.02 to 0.18	0.036

Year coefficient is the slope of the pre-intervention regression line; level coefficient = the predicted fall in the ASR immediately after the ARV programme was introduced; trend coefficient = the net change in the slope from before to after the intervention.

Conveniently, the Standard Population sums to 100,000. The calculation of the ASRs was carried out according to the recommendations of the International Agency for Research on Cancer (IARC) (Jensen et al., 1991). The formula used is as follows:

$$ASR = \frac{\sum_{i=1}^{18} a_i w_i}{\sum_{i=1}^{18} w_i}$$

where a_i is the age group-specific incidence rate per 100,000 for the ith age group class, and w_i is the population present in the ith age group class of the Standard Population.

The complete record of submissions is used for the estimation of the ASRs. The estimation of the variances for the ASRs uses the following formula:

$$Var(ASR) = \frac{\sum_{i=1}^{18} \left[a_i w_i^2 (100\ 000 - a_i)/n_i \right]}{\left(\sum_{i=1}^{18} w_i \right)^2}$$

where n_i is the person-years of observation for the ith age group. The normal approximation 95% Confidence Intervals were then calculated using the formula:

$$ASR \pm 1.96 \sqrt{Var(ASR)}$$

The ITSA was performed using R statistical software, version 3.6.5. Statistical significance was determined at $p \leq 0.05$. Graphs were prepared using Stata version 16. On inspection of graphs of ASRs plotted against years, a period between 2008 and 2009 was noticed before the slope changed. This was the case for both female and male cases. Hence, both sex-specific ITSA models that were estimated assumed a turning point mid-way between 2008 and 2009. The changes in the female and male ASRs, both the immediate effect on these rates as well as their rates of change, were estimated. The pre-turning point ASRs were projected forward to estimate counterfactuals for the post-turning point trends. The pre-ART-era linear regression lines (up to and including 2008) were projected to the post-ART period to provide the expected trend without the intervention (i.e. the counterfactuals).

The Durbin–Watson test was used to test for autocorrelation using up to five lag periods, as were plots of the autocorrelation function (ACF) and partial autocorrelation function (PACF).

Table 5
Model selection criteria for the female data and male data models.

	Female data			p-value		Male data			p-value
	AIC	BIC	LL	vs. OLS	vs. AR(5)	AIC	BIC	LL	vs. OLS
Ordinary least squares models	26.05	30.51	−8.03			39.41	43.86	−14.70	
AR(5) model	21.09	29.99	−0.54	0.011					
Trend-squared models	23.42	28.76	−5.71	0.031	0.035	35.06	40.41	−11.53	0.012

AIC = Akaike information criterion; BIC = Bayesian information criterion; LL = log likelihood; OLS = ordinary least squares; AR(5) = autoregressive model with 5-period autocorrelation.

Regression models were prepared separately for females and males. Ordinary least squares models, autoregressive models (if indicated) and models incorporating a post-turning point trend-squared term were compared with each other by using the likelihood ratio test. The final selection of the best models was guided by the results obtained for the model AIC (Akaike information criteria) and BIC (Bayesian information criteria) statistics, as well as the log likelihood statistics for the models. For the males and females, the models with the lowest AIC and the lowest BIC, as well as the highest log likelihood, were deemed to be the best-fitting models.

The outcome variable for all the models was the ASR per 100,000 person-years. The predictor variables that were included were Time (the year, with 1999 coded as 1, 2000 as 2, etc. up to 18 in 2016); Level (level = 0 prior to the turning point and 1 after the turning point); and Trend (trend = 0 prior to the turning point, 1 in 2009, 2 in 2010, etc. up to 8 in 2016). In the models that include a squared term for the post-intervention predictions, an additional variable, Trend-squared, was included.

Results

The total number of cases of KS in the black population group was recorded as 29,263 from 1999 to 2016 in the pathology-based registry. Black female KS patients numbered 12,457, while black male KS patients numbered 17,166. Figure 1 shows a time series graph of the number of cases for the black females and black males between 1999 and 2016. The graph shows that there was an increasing trend in the number of cases reported between 1999 and 2008. From 2009, there was a decrease in the numbers of cases each year.

Table 2 shows the age-specific crude and age-standardised incidence rates by sex.

For the female data set, the Durbin-Watson test for autocorrelation was significant ($p = 0.002$) for a 5-period lag. This was confirmed on inspection of the ACF and PACF residuals plots. For the male data set, there were no statistically significant results for the Durbin–Watson test and there were no statistically significant spikes in the ACF and PACF plots. The ASCF and PACF plots are presented as supplementary material. An AR(5) (autoregressive) model was prepared for the female model.

The results for the regression models are presented in Table 3 for the female data set and Table 4 for the male data set. The values for the AIC, BIC and log likelihood for these models are presented in Table 5. For the female results, it is clear from Table 5 that the linear model incorporating a correction for autocorrelation, the AR(5) model, was the best-fitting of the three models as, of the three, it had the lowest values for AIC and the highest log likelihood value. The BIC values for the three models were similar. Furthermore, the likelihood ratio tests gave a p-value of 0.011 for the AR(5) model vs. the linear model that assumed no autocorrelation and 0.035 for the comparison with the quadratic model.

This autoregressive model was used to estimate the impact at five years for the data for females. Graphs of the fitted values for female ASRs against time are presented as Figures 3–5.

For the male cases, there was no statistically significant autocorrelation detected by the Durbin–Watson test, and there were no significant spikes in the ACF/PACF plots. As a result, no model was prepared with adjustments for autocorrelation.

The results for these two models for the male data set are presented in Table 4. It is apparent that the model that incorporates a quadratic fit for the post-intervention has the best fitting parameters. It had the lowest AIC and BIC and the highest log likelihood of the models. The likelihood ratio test comparing this model with the OLS model provided a p-value of 0.012, indicating that the difference between these two models is statistically significant. Therefore, the quadratic model was used to estimate
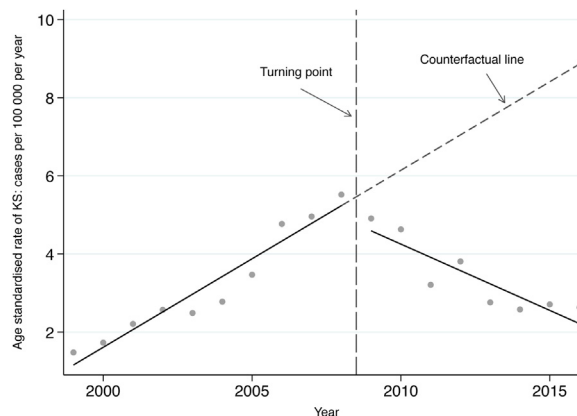

Figure 3. The fitted regression lines (female cases) ordinary least squares model.
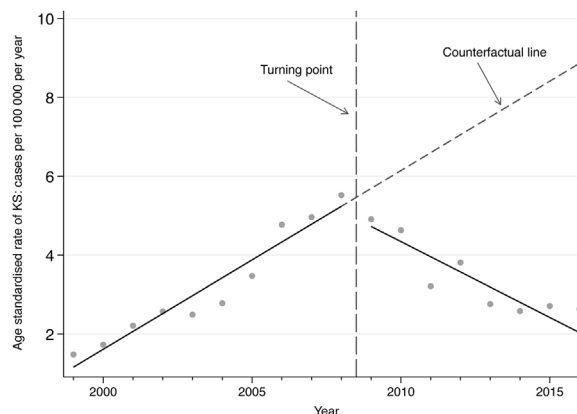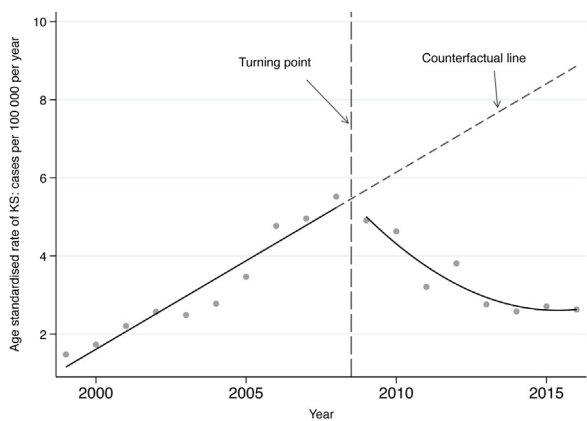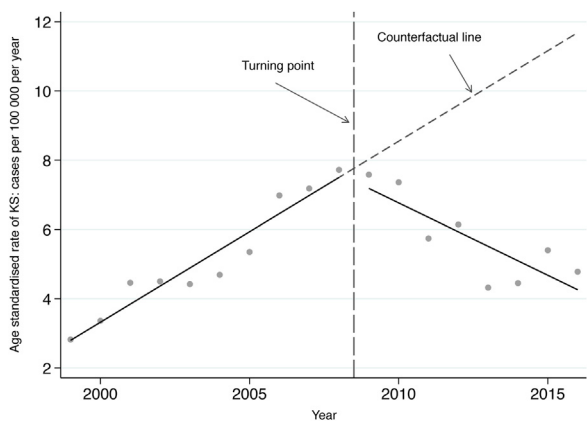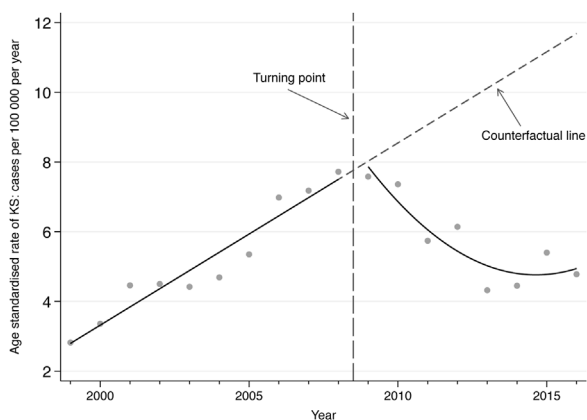

Figure 4. The fitted regression lines (female cases) adjusted for five time-period autocorrelation.

Figure 5. The fitted regression lines (female cases) with a quadratic post-turning-point segment.

Figure 6. The fitted regression lines (male cases) ordinary least squares model.

Figure 7. The fitted regression lines (male cases) with a quadratic post-turning-point segment.

the five-year impact of the programme for males. Graphs of the fitted values plotted against time are presented as Figures 6 and 7.

All the models showed that there was no immediate, statistically significant drop in ASRs for either females or males in 2008 for any of the models.

Regarding the changes in the ASRs over time, the post-2008 rates of decline were compared to the counterfactual rates of increase, which were presumed to be the same as the rates of

increase that prevailed prior to 2009. These net changes in rates were found to be −0.86 cases per 100,000 per year (95% CI −0.93 to −0.79; $p < 0.001$) for female cases (autoregressive model) and −1.82 cases per 100,000 per year (95% CI −2.58 to −1.06; $p < 0.001$) for male cases (quadratic model).

However, as the selected model for males portrays the decline in cases as having a quadratic relationship with time, these values for male cases only apply in the immediate post-2008 moment; the relative decline would be lower as time progresses, and the curve for predicted male cases flattens out.

The estimates for the 2013 reduction in the ASRs are presented in Table 6. These reductions are equivalent to 58.3% for the female data set and 50.3% for the males. Based on the estimated reduction in ASRs and the mid-year population estimates for 2013, this represents a reduction of 967 female black age-standardised cases (95% CI 839–1094) and 1049 male black age-standardised cases (95% CI 783–1237) in 2013.

Discussion

To our knowledge, this study is the first to report on the impact of the national ART rollout on the KS incidence rates in SA using ITSA. Indeed, we have not seen any similar approach used in other African countries either. Estimating the impact of ART on the incidence of KS (and other HIV-related illnesses) is important as ITSA provides more realistic estimates of the impact of ART than simple before and after comparisons that do not take into account what the incidence might have been without the intervention. Such impact studies may be used for economic evaluation studies or to advocate for extension or intensification of efforts to widen the uptake of ART at an earlier stage among people living with HIV.

This study found that the ASR for KS declined after 2008 and that there was a four-year period from start of ART programme in 2004 and a noticeable turning point between 2008 and 2009. Potentially, there has been a 58% decrease in the ASR for black females, compared to what would have been expected in the absence of the ART intervention, and a 50% decrease in black males, nine years after the launch of the ART programme. This reduction of the ASRs does not approximate reported declines elsewhere in Africa following the introduction of ART (even allowing for the fact that those reductions were not estimated using ITSA and are, therefore, likely to be underestimates of the impact of ART on KS incidence), such as a reduction from 32 cases per 100,000 to 4.9 cases per 100,000 (Sitas et al., 2008).

Had we not used ITSA, but merely compared the cases in 2008 to those in 2013, we would have noted a reduction of only 2535 − 1541 = 994 cases (see Table 2 data). Hence, we would have underestimated the impact of the ART programme by over 50%.

We carried out our analysis using the pre-2008 ASRs projected forward to the post-2008 time period as predicted counterfactual ASRs. We did not have a suitable (external) control group for our analysis as we did not have any concurrent data for ASRs in an ART-naïve population for comparison purposes.

As we used the routinely collected NCR data, we were limited to some extent by the lack of information, at an individual level, regarding possible confounders. The CD4+ count, because it has been used to select people for ART, is one such possible confounder that we have not taken into account in our analysis.

In their study, Sengayi et al. (2017) noted that 25% of their HIV sero-positive KS patients had a previous history of tuberculosis. This history would have made them eligible for ART irrespective of CD4+ cell counts, provided that the illness occurred within two years prior to the diagnosis of HIV.

Furthermore, it is noteworthy that only 12% of their KS patients, diagnosed during 2004–2008, had never received ART (although many were no longer taking ART at the time of KS diagnosis). For

Table 6
Estimated reduction in the ASRs for the different models.

Model	OLS	Autoregressive	Trend-squared
Female date set			
Counterfactual predicted (95% CI)	7.50 (6.58–8.42)	7.65 (7.18–8.12)	7.50 (6.66–8.34)
Fitted based on the observed data (95% CI)	3.24 (2.94–3.54)	3.19 (2.83–3.54)	2.94 (2.53–3.35)
Estimated reduction (95% CI)	4.26 (3.36–5.16)	4.46 (3.87–5.05)	4.56 (3.63–5.49)
Male data set			
Counterfactual predicted (95% CI)	10.11 (8.78–11.44)		10.11 (8.95–11.27)
Fitted based on the observed data (95% CI)	5.51 (5.07–5.95)		5.02 (4.46–5.58)
Estimated reduction (95% CI)	4.60 (3.20–6.00)		5.09 (3.80–6.38)

CI = confidence interval; OLS = ordinary least squares model; trend-squared = OLS model that includes the trend squared covariable.

the patients diagnosed between 2009 and 2012, only 2.5% had never received ART. It would appear, therefore, that failure to meet the required CD4+ count to qualify for initiation of ART has not been a substantial barrier to ART access, although the duration of prior ART treatment was not reported.

The possible confounding effect of delayed initiation of ART is that ART would be reserved for those with lower CD4+ cell counts, and ART initiation would therefore have occurred too late to prevent the occurrence of some cases of KS. This would lead to an underestimation of the potential benefit of introducing ART if it is started early and if treatment is sustained.

For these reasons, we should regard our estimates of cases prevented as "minimum" estimates of the potential impact of ART.

Between 1999 and 2016, there was, approximately, a 30% increase in the HIV burden of disease in South Africa, as is evident from inspection of Figure 2. This increase in HIV prevalence may have been partly due to new cases, but also due to longer survival as more people gain access to ART.

To the extent that the increasing prevalence of HIV is partly due to new cases where ART may not yet have been started, this rising prevalence would be expected to result in a rising ASR for KS throughout the study period.

With the introduction of the universal ART treatment strategy in 2016, further decreases in HIV-related cancers are expected as access to ART, earlier on, increases. This can be explored in future studies when sufficient data are available.

This study has a number of important limitations. Confounding cannot be completely ruled out as we were not able to incorporate a suitable control group into the analysis and also because we do not have information about potential confounders such as the CD4 + cell count. There may also be other unknown confounding variables that we have not been able to incorporate into the analysis. This study made use of a single-group ITSA design which used extrapolation of the pre turning-point trends to the post-turning-point period as the counterfactual.

Another limitation is the possibility of under-reporting to the NCR. This will affect estimates of the number of cases prevented. For the period of this study, the NCR data were based on pathology-confirmed cancers reported to the NCR by the country's laboratories. Cancers diagnosed solely on radiology or clinical examination were not included in this study, although the reports available for South Africa (Sengayi et al., 2017; South African National cancer Registry, 2018; International Agency for Research on Cancer, accessed 2020) would suggest that the proportion of KS tumours that are subjected to histology in South Africa is high. Still, the possibility remains that some patients with KS may not make contact with the formal health services, and, if they do seek care, may not have biopsies taken and sent for analysis.

The validity of this analysis also depends on the completeness and consistency of reporting to the NCR over the years of the study. During the period 2004–2010, some private laboratories did not submit data to the NCR, as reporting to the NCR was, at that time,

voluntary (Singh et al., 2015). This may have led to underestimation of ASRs for KS for the affected years. However, the NCR has demonstrated that, while the reporting in the private sector decreased between 2005 and 2007, overall cancer reporting was minimally affected with a net decrease in reporting of <4%. In addition, as under-reporting was mainly from the private sector and as most black South Africans accessed healthcare in the public healthcare sector, we are confident that the ASRs for black South Africans were not greatly affected by under-reporting during this period.

The fact that 64% of the HIV positive patients diagnosed with KS in the study by Sengayi et al. were already taking ART at the time of diagnosis suggests that some people with HIV infection may be starting treatment too late to prevent HIV-related KS. The proportion of HIV sero-positive South Africans who were taking ART in 2016 was estimated at approximately 50% (Figure 2). While there has been a substantial reduction in the number of new cases experienced due to the ART programme, the full benefits to society will only be experienced once the proportion of people with HIV that are taking ART is greatly increased. Furthermore, ART needs to be started early enough to prevent the occurrence of KS.

Finally, the ASR estimates and their 95% Confidence Intervals, as presented in Table 2, were calculated according to the recommendations of IARC, and they were obtained without taking in to account possible clustering by region. As a result, the 95% Confidence Intervals that are presented may be too narrow.

Conclusions

This ITSA has demonstrated a substantial reduction of the ASRs for KS among black females and males in South Africa, nine years after the introduction of the national ART programme. These reductions are of the order of 58% and 50% for females and males, respectively, and they occurred in spite of an ART coverage of only approximately 40% among people living with HIV in that year in spite of this low coverage. Nevertheless, judging by what has been achieved elsewhere in Africa, there is much room for improvement. Measures to increase ART initiation among those people infected with HIV and to do so as early as possible should be intensified.

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Ethical approval

The investigators obtained ethical approval from the University of Pretoria's Faculty of Health Sciences Research Ethics Committee (FHSREC) (49/2019).

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2020.10.020.

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