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Research Highlights

- Evidence of HIV incidence decline in the population of Eshowe/ Mbongolwane
 - Highest HIV incidence decline (>50%) in women 20-29 years between 2013 and 2018
 - No evidence of HIV incidence decline for women in the age group 15-19
 - Insufficient power to detect incidence change in men for age group 20 -29
- Population surveys should focus resources on women aged 15-19

Journal Pre-proof

Evidence of HIV incidence reduction in young women, but not in adolescent girls, in KwaZulu-Natal, South Africa

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Abstract

Objective

We estimated changes in the HIV incidence from 2013 to 2018 in Eshowe/Mbongolwane, KwaZulu Natal, South Africa where Médecins Sans Frontières is engaged in providing HIV testing and care since 2011.

Methods

Using data from two cross-sectional household-based surveys conducted in 2013 and 2018, with consenting participants aged 15-59 years, we applied the incidence estimation frameworks of Mahiane et al and Kassanje et al.

Results

In total 5599 (62.4% women) and 3276 (65.9% women) individuals were included in 2013 and 2018 respectively. We found a mean incidence in women 20-29 years of 2.71 cases per 100 person-years (95% CI: 1.23; 4.19) in 2013 and 0.4 cases per 100 person-years (95% CI: 0.0; 1.5) in 2018. The incidence in men 20-29 years was 1.91 cases per 100 person years (95% CI: 0.87; 2.93) in 2013 and 0.53 cases per 100 person-years (95% CI: 0.0; 1.4) in 2018. The incidence decline among women aged 15-19 was -0.34 cases per 100 person-years (95% CI: -1.31; 0.64).

Conclusions

The lack of evidence of incidence decline among adolescent girls is noteworthy and disconcerting our findings suggest that large scale surveys should seriously consider focusing their resources on the core group of women aged 15-19.

Keywords: HIV, incidence, prevalence, recency tests, ART, cross-sectional surveys

Introduction

HIV prevalence is a complex emergent indicator which depends in detail on a long history of incidence and survival, hence changes in HIV prevalence over time do not reflect the trends in incidence and incidence differences. The monitoring and evaluation of HIV interventions and programmatic investments requires metrics and benchmarks that demonstrate progress in the AIDS response [1], [2]. They are essential to monitor HIV transmission and to guide HIV prevention, in order to ensure that the priority groups are identified and reached [3]. Those metrics include, among others, the absolute rate of HIV incidence and percentage reduction in new HIV infection.

It has been reported that the rate of new HIV infections in the general population is declining in eastern and southern Africa over the last decade [2]–[4]. However, few studies that used disaggregated data for age and sex to estimate HIV incidence showed that findings differed according to the different sub-groups [5]–[7]. For instance, adolescent girls and young women still experience high risk of HIV infection compared to other sub- groups.

Furthermore, while most of the studies use longitudinal cohort methodology to estimate the incidence, population-based cross-sectional methodology started being exploited in the last recent years to provide incidence results, using biomarkers of ‘recent infection’, combining Lag-Avidity and viral load results to define recent infection, and adapting the method for age-specific incidence estimation [7]–[9].

However, while there has been some progress in the use of data from population-based surveys to estimate HIV incidence, a consensus is yet to be reached on how to analyse and interpret the population based survey data meant for HIV incidence estimation. Some reliable and rigorous methods for using survey data rely on careful analysis of 1) age and time structure of prevalence in the Mahiane method, and 2) prevalence of recent infection in the Kassanje method. Very little work has been done on the optimal characterisation of the

age and time structure of survey data, and from there, the optimal combination of the Mahiane and Kassanjeer methodologies.

Médecins Sans Frontières is engaged since 2011 in a long-term community level HIV prevention and treatment programme in the Eshowe/Mbongolwane sub-district in the KwaZulu Natal province of South Africa, a region severely affected by the HIV pandemic [10]. A major population-based survey was conducted in 2013 [11], the survey gave the opportunity to use a novel hybrid method to estimate HIV incidence by age and sex in the sub-district [9]. A similar survey was implemented in 2018 [12]. Its results showed a significant increase of viral load suppression among HIV-positive individuals between 2013 and 2018 (57.1% and 83.8% respectively, $p < 0.001$). Moreover, all subpopulations of HIV-positive individuals, had a proportion of viral suppression $> 72.5\%$ in 2018 except men aged 15–29 with 51.5% [12].

The optimal characterization of incidence in the period 2013 to 2018 is key to an understanding of the impact of HIV in the community hosting this large MSF programme and holds clear lessons for the epidemiological surveillance community generally. We report in this paper 1) findings on incidence in 2013 and 2018 as relates to age and sex in Eshowe/Mbongolwane sub-district. These findings provide valuable insights and lessons for the epidemiological surveillance community; 2) crucial analytical lessons to consider in major HIV surveys, and 3) limitations which must be faced both in our specific context and in the surveillance of HIV incidence more broadly. These limitations highlight the challenges that must be acknowledged and overcome for enhanced HIV incidence surveillance.

Methods

Two cross-sectional household-based surveys using a two-stage cluster sampling and including ascertainment of HIV status and ‘recent infection’ status, were conducted in 2013 [11], and 2018 [12] in Eshowe/ Mbongolwane sub-district. In both years, recruitment of

survey participants occurred among consenting residents of the survey area and visitors who had spent at least the previous night in the survey area. Using a serial testing algorithm, HIV testing was proposed to all survey participants, irrespective of knowledge of HIV status or current ART use, at their residence with an HIV rapid test using whole blood obtained by finger-prick. Participants positive on both tests were considered positive. Those with discordant results had a third “tiebreaker” test to confirm the HIV status using ELISA in 2013 [11] and a Western Blot platform (Bio-Rad, USA) in 2018 [12]. The detailed laboratory algorithms have been described elsewhere [11], [12]. Additional laboratory-based tests were performed concurrently to conduct HIV- ribonucleic acid (RNA) viral load (VL) and ‘recency’ testing by Maxim/Sedia Limiting Antigen ELISA (LAg-Avidity test). In both years, individuals willing to participate in the survey without receiving the HIV test on site, had blood collected for HIV, HIV-RNA VL and LAg-Avidity tests that were conducted at laboratory level.

Definitions

We defined ‘viral suppression’ as HIV-RNA VL below 1000 copies/mL and “a positive “recency” test as individuals with a HIV-RNA VL > 75 copies/mL and a normalised optical density ≤ 2.0 on LAg-Avidity test.

Data collection and analysis

Data were captured from paper-based questionnaires, laboratory information management systems and registers according to the standard procedures of each laboratory. Questionnaires were pre-tested prior to the studies’ launches. Data were double entered into EpiData 3.1 (EpiData Association, Odense, Denmark) and statistical analyses were performed with STATA 14 and 15 (StataCorp, College station, Texas, USA) and R [13]. In 2013, participants aged 15 to 59 years were eligible to participate in the survey, while in 2018, the survey

targeted individuals aged 15 years and older [11]. To allow comparisons, we included in the analysis participants aged 15–59 years only from both surveys.

Statistical methodology

The fundamental components of the analysis relevant to such data sets can be performed using the R package *inctools*, which is maintained by two of the present authors [14].

We fitted the HIV status data to generalised linear models regressing HIV and HIV “recency” status on age and time, according to methods described in detail in our methodological investigation [15] leading to estimates of prevalence of HIV infection, and prevalence of ‘recent infection’ among HIV infected individuals being available as continuously specified functions of age and time. The Mahiane estimator [16] (Equation 1, in the supplementary material) was evaluated, using as inputs: the infection prevalence function and its time/age gradient, and an estimate of ‘excess mortality’ from the Thembisa HIV model [17]. This leads to a continuously specified incidence estimate I_M for a range of values of age and time. Similarly, the Kassinjee estimator [18] (Equation 2, in the supplementary material) was evaluated, using as inputs: the infection prevalence function and the recency prevalence function, and an estimate of ‘recency test’ Mean Duration of Recent Infection and False Recent Rate of 190 days 95% CI (173 - 207) and 0.2% 95% CI (0.1-0.4), respectively [19], [20]. This leads to a continuously specified incidence estimate I_K for a range of values of age and time.

The optimally weighted incidence estimator is derived from using the inverse variance method, the estimated to yield I_{Opt} (Equation 3, in the supplementary material). The variance covariance structure of I_M and I_K was estimated by bootstrapping of data in accordance with the sampling design and obtaining a continuously specified age/time dependent optimally weighted estimate. The continuous age dependent incidence differences (2013-2018) and their uncertainty was calculated by evaluating difference point estimates within each data

bootstrap iteration. Also, within each bootstrap iteration, we used the age/time specific distribution, incidence and incidence difference estimates to calculate the weighted incidence and incidence difference in each age group, as well as their confidence intervals, and p-values for test of equality between 2013 and 2018.

The estimates for similar ages are highly correlated, as they are based on smoothing the same dataset. However, each age specific estimate does add a little more information, so we averaged over some age groups to explore how this might increase the statistical significance. We should think of this procedure as ‘reaggregating’ after having disaggregated the estimates in the age specific smoothing process. The data allowed us to generate both prevalence and incidence estimates over a wide range of age groups. Incidence estimates derived for ages more than 30 became uninformative, with wide 95% CI. Hence, we present in this paper incidence results for individuals aged less than or equal to 30 when we display the overall incidence.

We examined the difference in incidence rates for specific age groups, which were categorized into 5-year intervals (15–19, 20–24, and 25–29) as well as a 10-year interval (20–29). These age groupings align with the standard age groups used in UNAIDS reports.

For each age group, the estimated incidence difference rate was compared to the central age-specific incidence difference rate. For instance, the central age for the 15–19 age group was 17. This comparison provided insight into whether the HIV incidence difference rate for the central age group was closer to the overall average or exhibited a skewed distribution within the age group. By analysing these comparisons, we gained a better understanding of the distribution patterns and variations in HIV incidence rates across different age groups.

P-value below 0.05 were considered statistically significant.

Results

In total, 5599 individuals were included in 2013 and 3276 in 2018, including 3492 women (62.4%) in 2013 and 2158 (65.9%) in 2018. Table 1 presents the total number of the population by 5-year age groups, as well as the distribution of HIV-positive and positive recency test among the two samples of 2013 and 2018, disaggregated by age groups and gender. High proportions of positive HIV tests were observed among women as compared to men: 24.7% in women and 16.0% in men in 2013, and 30.5% in women and 18.4% in men in 2018. The proportion of HIV positive recency tests was the highest among adolescent girls (15 – 19 years) in 2013 with 12.9%, and among men aged 20-24 years in 2018 with 20.0%.

Figure 1 shows the estimated HIV prevalence by age and gender for ages 15 to 35. In both years the prevalence increased with age in women and men, and the prevalence among women was higher than the prevalence among men, with the highest prevalence among the women aged 34 in 2013 (56.8%), and women aged 36 in 2018 (50.2%) The estimated prevalence in men remained low between the ages of 15 (1.79%) to 24 (7.74%), while the estimated prevalence among women exceeded 8.9% and 10% by age 18 in both 2013 and 2018, respectively.

Figure 2 presents incidence results using the Mahiane estimator, the Kassanjee estimator, and a variance minimizing linear combination method which is optimized for each integer age. The three distinctly coloured solid lines represents each incidence estimation method and the corresponding shading around the line is the respective confidence interval. For the optimally weighted estimator, the 2013 incidence in women was 1.31 cases per 100 person-years (95 % CI: 0.84;1.77) among 15 years old and 3.75 cases per 100 person-years (95 % CI :2.00; 5.51) among the 30-year-old with a peak of 4.17 cases per 100 person-years (95 % CI: 2.84;5.51) at 26 years. In 2018, we observed 0.98 cases per 100 person-years (95 % CI: 0.0; 2.00) at age 15, 1.64 cases per 100 person years (95 % CI: 0.0; 3.29) at age 30 , 0.96 cases per person years (95 % CI:0.0; 2.75) at age 26, and the peak incidence in 2018 was at age 22 with an incidence rate of 2.74 cases per 100 person-years (95 % CI: 1.12;4.37) (see Table S1 and S2 in the supplementary material for the tabular format of Figure 2).

The incidence estimates among men from all three estimators was extremely low and indistinguishable from zero for ages 15 to 22 and gradually increased thereafter, but remained uninformative.

As expected, the optimally weighted incidence estimator was an average of the Mahiane and Kassanjee estimators and hence the incidence estimates from the Mahiane and Kassanjee

estimators exhibited the same trend as the optimally weighted average in all years and both genders.

The mean incidence among women aged 15 to 19 years old was 1.44 cases per 100 person-years (95 % CI:0.89; 2) in 2013 and 0.64 cases per 100 person-years (95 % CI: 0.089;1.2) in 2018. The mean incidence for older women aged 20-29 years was 2.71 cases per 100 person-years (95 %: CI:1.23; 4.19) in 2013 and 0.4 cases per 100 person-years (95 % CI: 0.0; 1.5) in 2018.

The HIV incidence in men aged 15 to 19 years was 0.3 cases per 100 person-years (95 % CI: 0.044; 0.6) and 0.069 cases per 100 person-years (95 % CI: 0.0; 0.219) in 2013 and 2018, respectively. Men of the age group of 20 – 29 years had a mean incidence of 1.91 cases per 100 person-years (95 % CI: 0.87; 2.93) in 2013 and 0.53 cases per 100 person-years (95 % CI:0.0; 1.4) in 2018.

Figure 3 presents the HIV incidence changes by age between 2013 and 2018. The incidence estimators were colour coded as in Figure 2. The women's age specific incidence difference was uninformative (not distinguishable from zero) for ages 15 to 23, but in ages 24 to 26 there was evidence of a decline in incidence, for the Mahiane and optimally weighted incidence estimators whereas the Kassanje estimator remained uninformative until the age of 26 and above.

Overall, all three estimators detected an incidence difference for ages 26 and 27: 1) the Mahiane estimator estimated an incidence difference of -2.36 cases per 100 person-years (95 % CI:-4.2; -0.31) and -2.44 cases per 100 person-years (95 % CI: -4.76; -0.13) respectively; 2) while the Kassanje estimator estimated an incidence difference of -2.56 cases per 100 person-years (95 % CI:-5.06; -0.044) and -2.79 cases per 100 person-years (95 % CI: -5.34; -0.24) respectively. The optimally weighted estimator gave an average estimate of the two estimators, yielding -2.53 cases per 100 person-years (95 % CI: -4.46; -0.6) and -2.71 cases

per 100 person-years (95 % CI: -4.68; -0.7) respectively, and had a narrow interval compared to the two suggesting a more precise estimate.

Figure 4 presents the mean incidence difference by age groups as compared of the age specific incidence difference for the central age of the specific age difference for both women and men. For the selected age group substantial incidence difference was observed for women aged 25-29 years, independent of the incidence estimation method and all the estimates were comparable to each other. There was no evidence of an incidence decline in all the selected age groups in men due to limited data.

An incidence decline, of -2.12 cases per 100 person-years (95 % CI: -3.68; -0.43) ($p=0.0139$) among women aged 20 -30 was observed between 2013 and 2018, while data were insufficient to detect a change in incidence among men of the same age group ($p=0.258$). The incidence decline among women aged 15 – 19 was -0.34 cases per 100 person-years (95% CI: -1.31;0.64).

Discussion

Seroprevalence data from two cross sectional surveys done in Eshowe/ Mbongolwane sub-district was used to estimate incidence and incidence trends. The incidence and incidence trends estimates were based on the ‘recency’ approach (Kassanjee estimator), synthetic cohort (Mahiane estimator), and variance weighted average of the two methods. This approach first appeared in Grebe et al (2018) [9] using seroprevalence data from a single cross-sectional survey.

Our analysis highlights the incidence decline among young women aged 20-29 years, with particularly strong evidence of decline among those aged 25-30 years, for whom the point estimate corresponds to roughly a halving of the incidence from 2013 to 2018.

Similarly, there is evidence worth noting ($p < 0.05$) that incidence declined among women aged 20-24 years and among men of the same age group, though for the latter ones at a lower scale. We did not find evidence of incidence decline among men of other ages, nor among young adolescent women aged 15-19 years.

There was no evidence of an incidence decline among adolescent girls aged 15-19 years and given that the incidence was high in this group in 2013 and noting the strong decline in young women aged 20 to 30 years, this is disappointing and runs counter to what was expected.

Epidemiological implications:

These findings are in accordance with the previous studies that have shown a decline in the overall incidence rate which was mainly a result of the interventions programmes (for example DREAMS [6], [21], [22] implemented in the regions with high HIV prevalence and incidence, specifically in Eshowe/ Mbongolwane sub-district where MSF has been operating in the region for the past eleven years by implementing preventive activities, ART initiation and adherence counselling, and other interventions [12]. The high levels of viral suppression for this population (83.8% in 2018) [12] are likely to be a key cause of declining incidence where it has been observed.

The lack of significant incidence decline (and a point estimate of decline that is almost exactly zero) among adolescent girls aged 15 to 19 suggests that adolescent girls have about the same risk as ever, of encountering viraemic sexual partners and our findings are consistent with other studies [10], [23]. In addition, several studies, suggests that the high incidence rates observed among adolescent girls are as a result of the sex work and age disparate sexual relationships they have with older man which exposes adolescent girls and young women to high risk of HIV acquisition [23]–[27].

Despite high overall viral suppression in population in 2018, viral suppression was lower among men than women (72.9% vs 87.2%) and was low among the 15-19 years old (71.7%

(65.2- 77.5)), particularly among young men aged 15-29 years, with 51.5% (34.8-67.9) of them virally unsuppressed [12]. This may be one of the reasons why there was no evidence of incidence decline among adolescent girls.

There was no statistical evidence of decline of the HIV incidence among men. However, point estimates were lower in 2018 compared to 2013 though with large confidence intervals. We cannot be sure if HIV incidence did not really decline, or we did not have sufficient statistical power to show a decline of the incidence.

Methodological implications

The Mahiane estimator is most informative (precise) for younger ages but becomes less precise, providing no useful information for ages above 30. Whereas the Kassanje estimator contributes is more informative at older ages, typically at ages greater than 25 years. The research findings from Grebe et-al [9], indicated that the Mahiane estimator remains unaffected by variations of the externally estimated 'excess mortality' in what was considered reasonable range (from 50% to 200%) of the estimate we obtained from the Thembisa model [17].

We believe that the approach of obtaining age specific estimates through regression of the form we used here, followed by averaging over age groups, provides a readily adaptable near-optimal way of extracting the information content of complex survey datasets for example, datasets used in this analysis.

One should note that the delta method variance expressions for numerous components of the final complex age averaged estimates can be derived but, this streamlining has no benefit outside of numerically intensive exploratory/benchmarking calculations – whereas brute force bootstrapping, given contemporary computing capacity, can never be avoided for any real data sets.

Limitations

The study had limited sample sizes as compared to the country level surveys like Demographic Health Surveys and Population-based HIV Impact Assessments for which the methods are primarily meant for. Unfortunately, excess mortality data required by the Mahiane estimator was outsourced as previously discussed and not from the studies themselves which impacts the incidence estimation process, however previous studies [9] through sensitivity analysis on the excess mortality suggest an acceptable level of discrepancy is observed.

Unfortunately, there were few male respondents in our study which resulted in uninformative incidence and incidence difference estimates in the men group, and hence we could not provide insightful incidence trends results among men in Mbongolwane/Eshowe

Looking forward

Despite significant limitations posed by the modest sample size compared to major surveys sponsored by governments, reaping the benefits of extensive simulation-based investigation, we were able to extract nuanced age and gender disaggregation from our data to produce incidence estimates, and to resolve estimates, under conditions in which a less sophisticated approach would not have shed much light.

Adaptations of this analysis to other contexts are in the first instance expected to be primarily around HIV surveillance, but in principle this need not be a limitation.

We need to understand what more could be done to decrease the persistently unacceptably high incidence among adolescent girls – which flies in the face of numerous nominally positive developments and indicators. While preventive and medical interventions to early diagnose and treat HIV infection should continue to effectively maintain viral suppression, and then decrease HIV incidence, further efforts that ensure equity and equality of access to these interventions should be enhanced, to close these remaining gaps among women aged less than 20 years and men. Moreover, large scale surveys should seriously consider focusing

their resources on the core age group aged 15-19 and other populations at risk for example men who have sex with men.

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Declaration of interests

The authors have declared that no competing interests exist.

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Ethical Approval statement

Ethical approval of the two surveys was received from the University of Cape Town Human Research Ethics Committee (HREC reference 2013: 461/2012; and 2018: 320/2018), the Health Research Committee of the Health Research and Knowledge Management Unit in 2013 (HRKM 008/13) and the Provincial Health Research Unit of the KwaZulu Natal Department of Health (NHRD2018 Ref: KZ_201807_26). Additionally, the “Comité de Protection de Personnes,” Paris, France in 2013 (REF CPP: 12091) and the Médecins Sans Frontières Ethics Review Board in 2018 (Reference: ID1842) approved the respective surveys. Prior to participation, participants provided written informed consent (in English or isiZulu) in both surveys.

Author contribution

Conceptualization: LM, AW, EG, HH, GVN, LO, and NC

Formal analysis: LM, AW, and EG

Methodology: LM, AW and EG

Analysis and Visualisation: LM, AW, and EG

Validation of the underlying data: LM, AW, EG, HH, and NC

Writing – original draft: LM, AW, and NC

Writing – review & editing: All authors

Data sharing

Deidentified data from both 2013 and 2018, including the R code are available on request from the corresponding author.

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Table 1: HIV positive, and HIV positive ‘recency’ tests results by 5-year age groups and gender, Eshowe/ Mbongolwane, KwaZulu Natal, 2013 and 2018

| Age groups | 2013 | | | | | | 2018 | | | | | |
|------------|--------|--------------|----------------------------|-------|--------------|----------------------------|--------|--------------|----------------------------|-------|--------------|----------------------------|
| | Female | | | Male | | | Female | | | Male | | |
| | Total | HIV-positive | HIV positive recency tests | Total | HIV-positive | HIV positive recency tests | Total | HIV-positive | HIV positive recency tests | Total | HIV-positive | HIV positive recency tests |
| N | n (%) | n (%) | N | n (%) | n (%) | N | n (%) | n (%) | N | n (%) | n (%) | |
| 15-19 | 775 | 62 (8.0) | 8 (12.9) | 667 | 12 (1.8) | 1 (8.3) | 381 | 28 (7.4) | 4 (14.3) | 342 | 13 (3.8) | 4 (30.8) |
| 20-24 | 605 | 157 (25.9) | 9 (5.7) | 433 | 19 (4.4) | 1 (5.3) | 344 | 66 (19.2) | 2 (19.1) | 190 | 5 (2.6) | 1 (20.0) |
| 25-29 | 496 | 202 (40.7) | 10 (5.0) | 293 | 59 (20.1) | 5 (8.5) | 233 | 87 (37.3) | 1 (1.1) | 124 | 18 (14.5) | 2 (11.1) |
| 30-34 | 307 | 174 (56.7) | 0 (0.0) | 174 | 62 (35.6) | 0 (0.0) | 258 | 114 (44.2) | 2 (1.8) | 96 | 36 (37.5) | 0 (0.0) |
| 35-39 | 279 | 157 (56.3) | 3 (1.9) | 133 | 61 (45.9) | 0 (0.0) | 184 | 93 (50.5) | 0 (0.0) | 94 | 41 (43.6) | 0 (0.0) |
| 40-44 | 255 | 128 (50.2) | 0 (0.0) | 119 | 45 (37.8) | 1 (2.2) | 170 | 83 (48.8) | 0 (0.0) | 81 | 27 (33.3) | 2 (7.4) |
| 45-49 | 253 | 82 (32.4) | 1 (1.2) | 92 | 33 (35.9) | 0 (0.0) | 165 | 68 (41.2) | 1 (1.5) | 67 | 26 (38.8) | 0 (0.0) |
| 50-59 | 522 | 122 (23.4) | 3 (2.5) | 196 | 47 (24.0) | 0 (0.0) | 423 | 118 (27.9) | 0 (0.0) | 124 | 39 (31.5) | 1 (2.6) |

Figure 1 Estimated prevalence by age in women (left facet) and men (right facet) Eshowe/Mbongolwane sub-district, KwaZulu Natal, South Africa, 2013 and 2018.

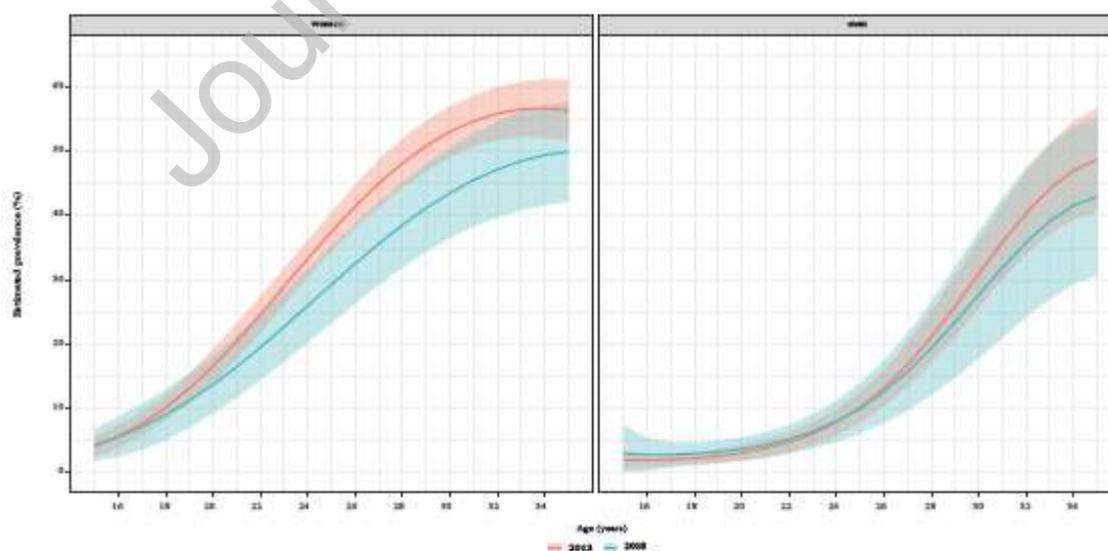


Figure 2 Age specific HIV incidence estimates by age from Eshowe/Mbongolwane sub-district, KwaZulu Natal, South Africa, 2013 and 2018

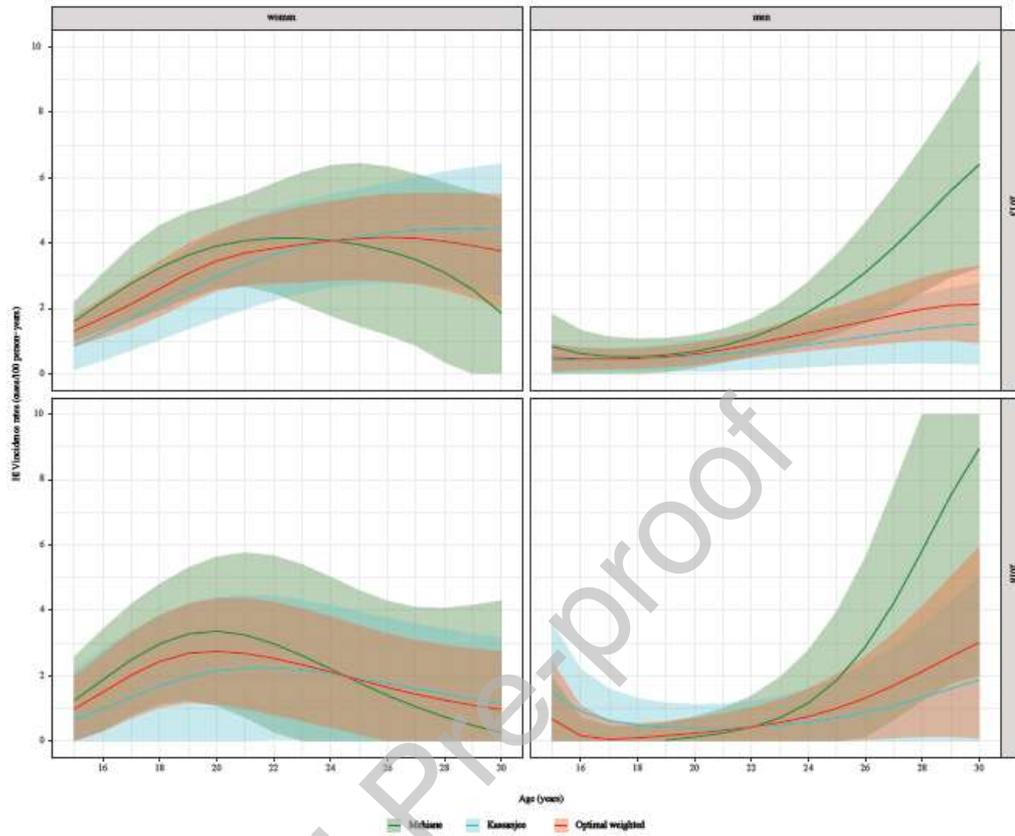


Figure 3 Age specific HIV incidence changes between 2013 and 2018, for both women (left facet) and men (right facet), in Eshowe/Mbongolwane, KwaZulu Natal, South Africa.

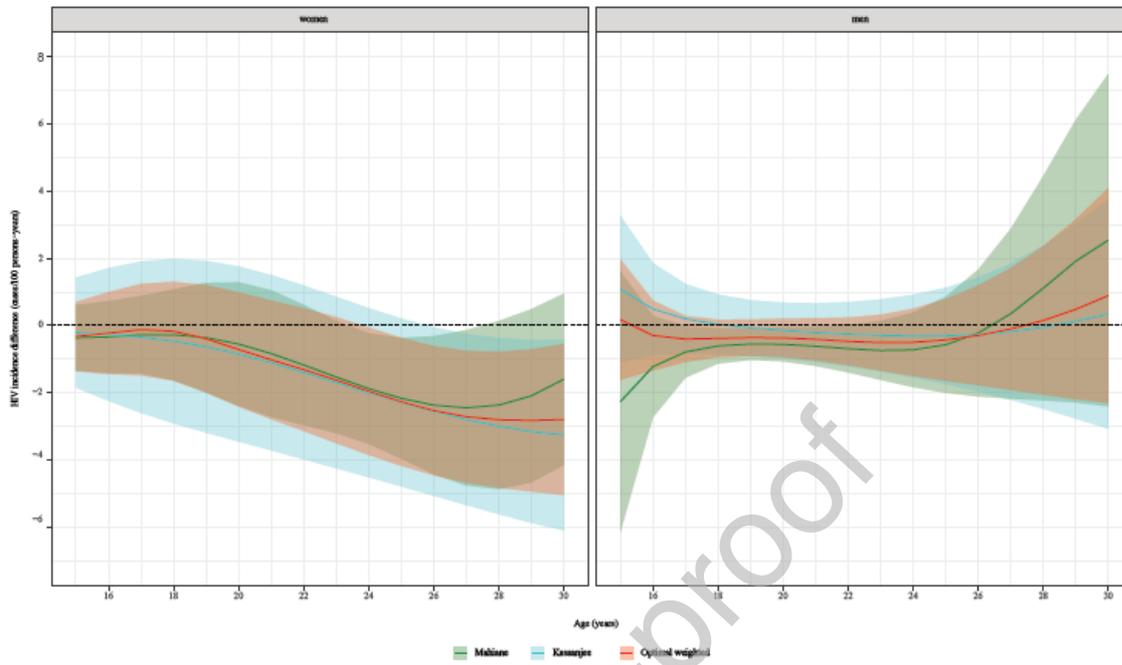
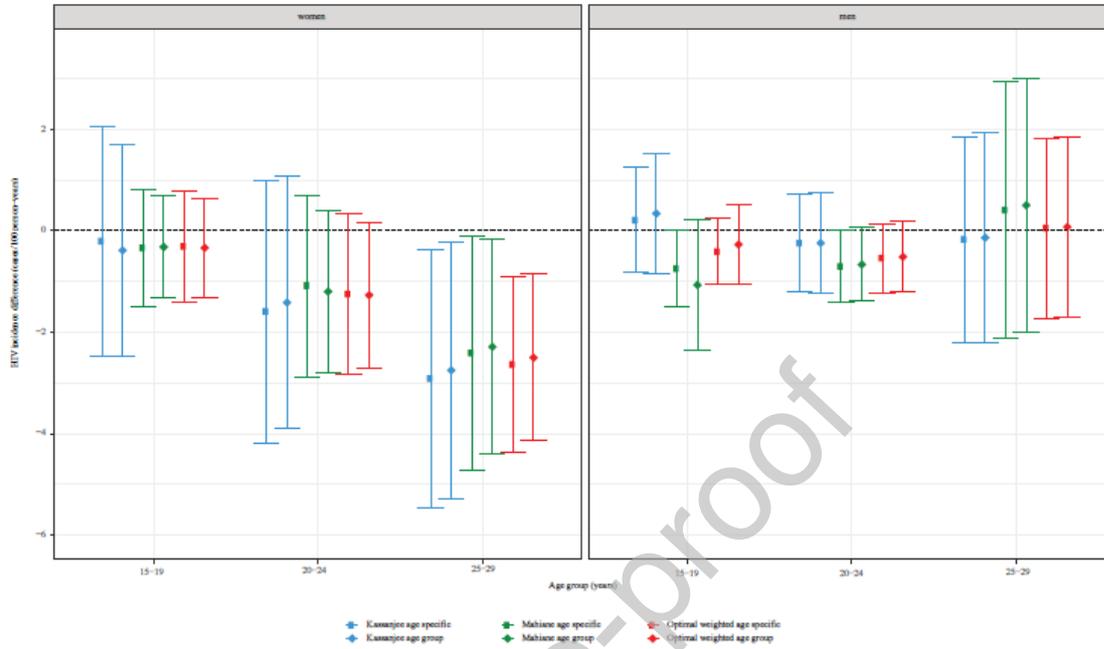


Figure 4 Mean HIV incidence changes by age groups between 2013 and 2018, women (left facet) and men (right facet), in Eshowe/Mbongolwane sub-district, KwaZulu Natal, South Africa.



Declaration of interests

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.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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