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

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ABSTRACT

Objectives: We estimated changes in the HIV incidence from 2013-2018 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 Kassanjee 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 aged 20-29 years of 2.71 cases per 100 person-years (95% confidence interval [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 aged 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 years.

Introduction

HIV prevalence is a complex emergent indicator that 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 require 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 infections.

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 subgroups [5–7]. For instance, adolescent girls and young women still experience a high risk of HIV infection compared to other subgroups.

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 limiting antigen (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 analyze and interpret the population-based survey data meant for HIV incidence estimation. Some reliable and

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rigorous methods for using survey data rely on careful analysis of (1) the age and time structure of prevalence in the Mahiane method, and (2) the prevalence of recent infection in the Kassanjee method. Very little work has been done on the optimal characterization of the age and time structure of survey data, and from there, the optimal combination of the Mahiane and Kassanjee methodologies.

Médecins Sans Frontières is engaged since 2011 in a long-term community-level HIV prevention and treatment program in the Eshowe/Mbongolwane subdistrict 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 subdistrict [9]. A similar survey was implemented in 2018 [12]. Its results showed a significant increase in 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 years with 51.5% [12].

The optimal characterization of incidence in the period 2013-2018 is key to an understanding of the impact of HIV in the community hosting this large Médecins Sans Frontières (MSF) program and holds clear lessons for the epidemiological surveillance community generally. We report in this study (1) findings on incidence in 2013 and 2018 as relates to age and sex in the Eshowe/Mbongolwane subdistrict; 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 the Eshowe/Mbongolwane subdistrict. 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 antiretroviral therapy (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 an enzyme-linked immunosorbent assay 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-RNA viral load (VL) and 'recency' testing by Maxim/Sedia limiting antigen enzyme-linked immunosorbent assay (LAg-Avidity test). In both years, individuals willing to participate in the survey without receiving the HIV test on-site, and 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 an HIV-RNA VL > 75 copies/ml and a normalized 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 before 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 15-59 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 generalized 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 Kassanjee 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% confidence interval (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, on the estimates 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 CIs, 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 >30 became uninformative, with wide 95% CI. Hence, we present in this study incidence results for individuals aged ≤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 Joint United Nations Programme on HIV/AID (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 analyzing these comparisons, we

Table 1
HIV-positive and HIV-positive 'recency' tests result 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)

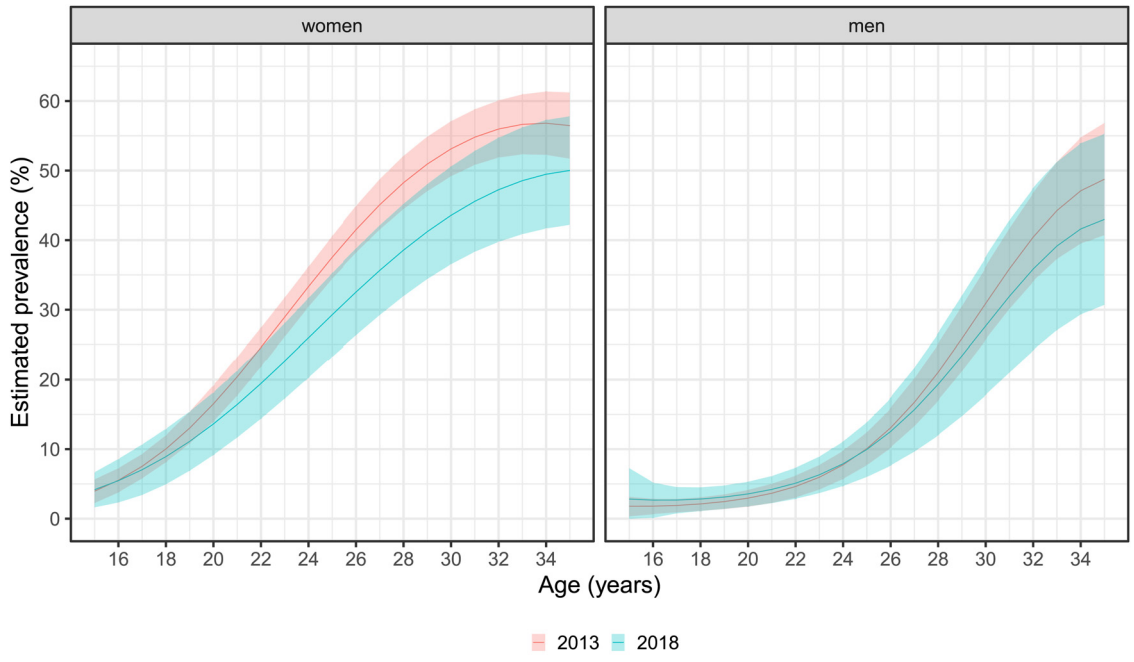

Figure 1. Estimated prevalence by age in women (left facet) and men (right facet) Eshowe/Mbongolwane sub-districct, KwaZulu-Natal, South Africa, 2013 and 2018.

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 at 12.9% and among men aged 20-24 years in 2018 at 20.0%.

Figure 1 shows the estimated HIV prevalence by age and gender for ages 15-35. 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 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 colored solid lines represent each incidence estimation method and the corresponding shading around the line is the respective CI. 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 Tables S1 and S2 in the Supplementary Material for the tabular format of Figure 2).

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

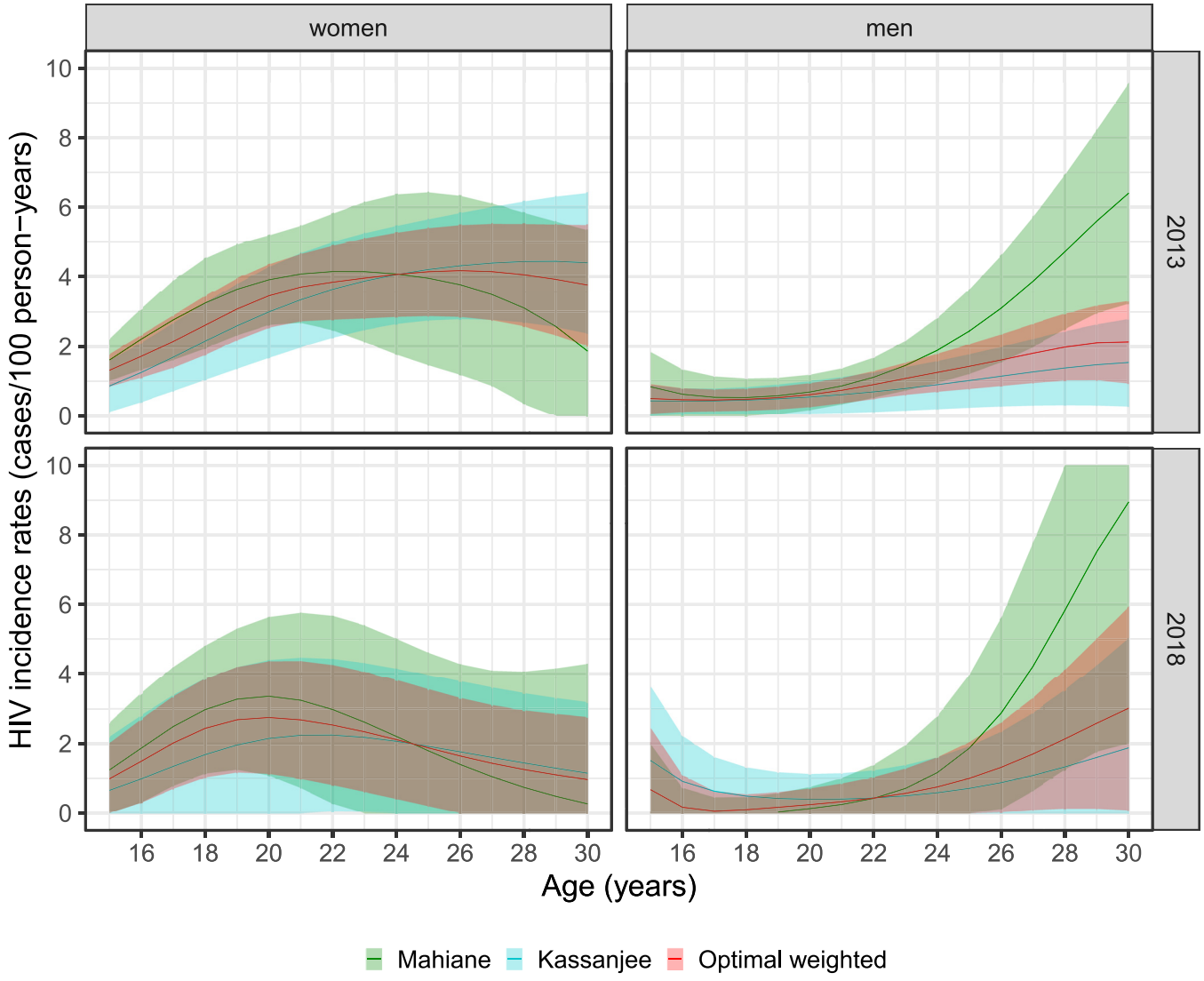

Figure 2. Age-specific HIV incidence estimates by age from Eshowe/Mbongolwane subdistrict, KwaZulu-Natal, South Africa, 2013 and 2018.

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 15-19 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 15-19 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 color coded as in Figure 2. The women's age-specific incidence difference was uninformative (not distinguishable from zero) for ages 15-23, but in ages 24-26 there was evidence of a decline in incidence, for the Mahiane and optimally weighted incidence estimators whereas the Kassanjee estimator remained uninformative until the age of 26 and above.

Overall, all three estimators detected an incidence difference for women aged 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 Kassanjee 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 to 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

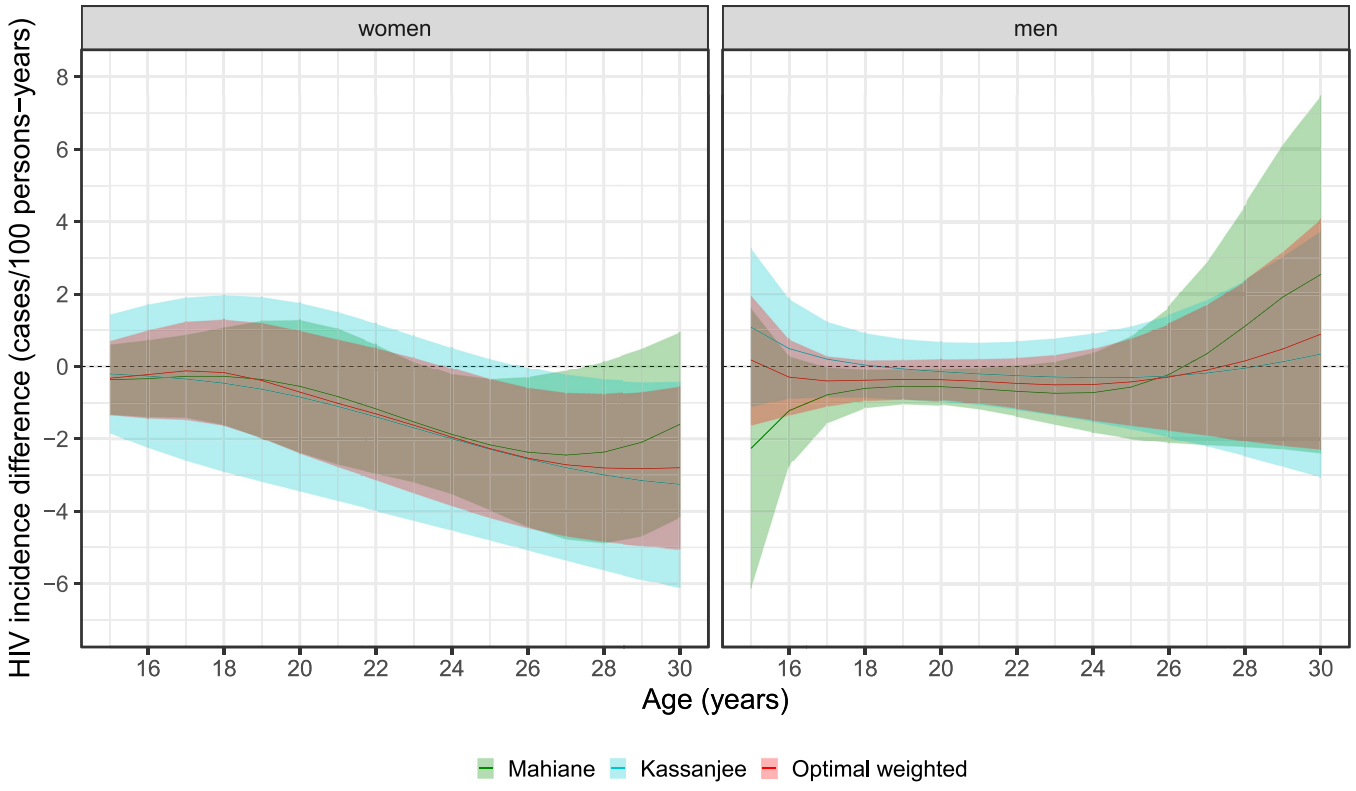

Figure 3. Age-specific HIV incidence changes between 2013 and 2018, for both women (left facet) and men (right facet), in Eshowe/Mbongolwane, KwaZulu-Natal, South Africa.

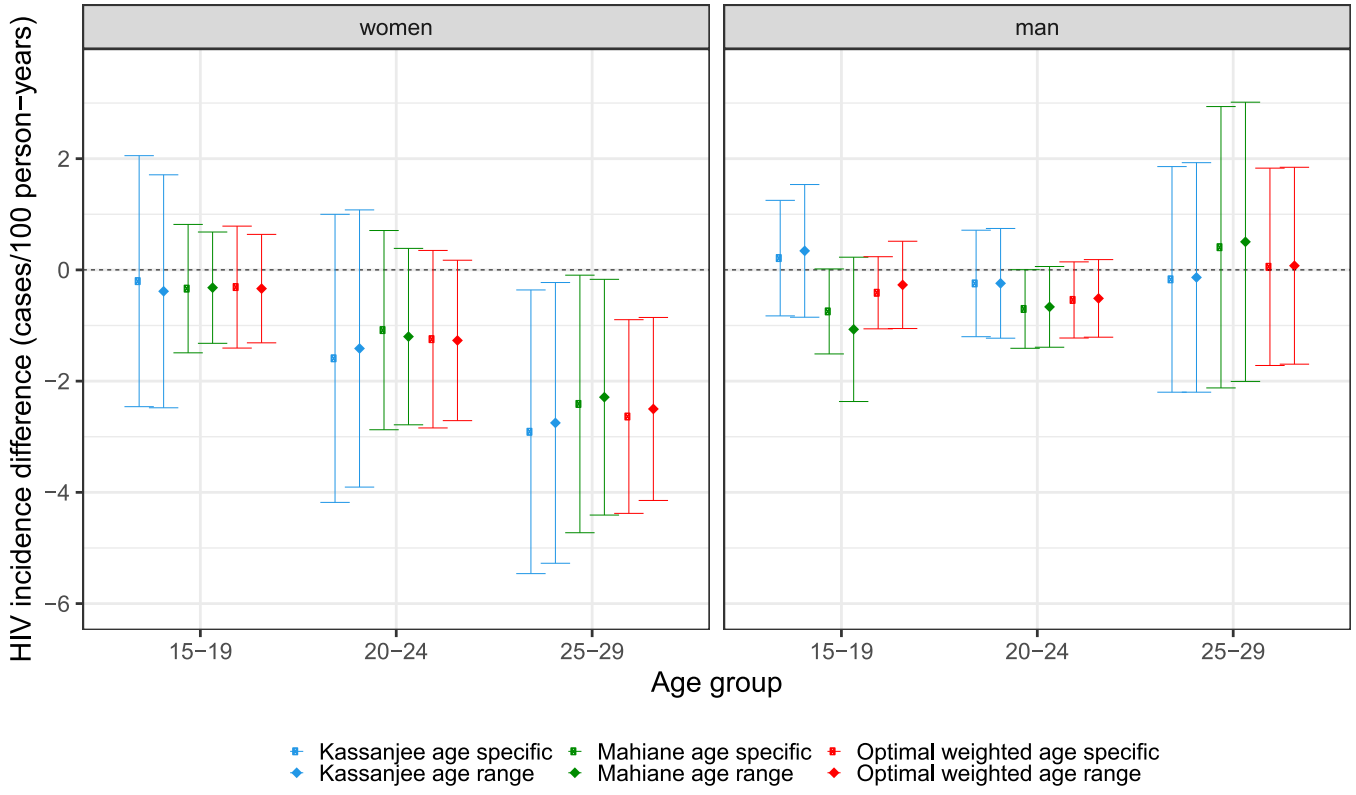

Figure 4. Mean HIV incidence changes by age groups between 2013 and 2018, women (left facet) and men (right facet), in Eshowe/Mbongolwane subdistrict, KwaZulu-Natal, South Africa.

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 subdistrict 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. [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 2013-2018.

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 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 20-29 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 programs (for example Determined, Resilient, Empowered, AIDS-free, Mentored and Safe (DREAMS) [6,21,22] implemented in the regions with high HIV prevalence and incidence), specifically in Eshowe/Mbongolwane subdistrict where MSF has been operating in the region for the past 11 years by implementing preventive activities, ART initiation, and adherence counseling, 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 15-19 suggests that adolescent girls have about the same risk as ever, of encountering viremic sexual partners and our findings are consistent with other studies [10,23]. In addition, several studies suggest that the high incidence rates observed among adolescent girls are a result of the sex work and age-disparate sexual relationships they have with older men which exposes adolescent girls and young women to high risk of HIV acquisition [23–27].

Despite high overall viral suppression in the 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 in HIV incidence among men. However, point estimates were lower in 2018 compared to 2013 though with large CIs. We cannot be sure if HIV incidence did not really decline, or if we did not have sufficient statistical power to show a decline in 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 years. Whereas the Kassanjee estimator 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 50-200%) 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 trend 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. Although 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 younger than 20 years and men. Moreover, large-scale surveys should seriously consider focusing their resources on the core age group aged 15-19 years and other populations at risk for example men who have sex with men.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

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 MSF Ethics Review Board in 2018 (Reference: ID1842) approved the respective surveys. Before participation, participants provided written informed consent (in English or isiZulu) in both surveys.

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Author contributions

Conceptualization: LM, AW, EG, HH, GVN, LO, and NC; Formal analysis: LM, AW, and EG; Methodology: LM, AW, and EG; Analysis and visualization: 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.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2023.07.004.

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