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Reply to ‘Should biomarker estimates of HIV incidence be adjusted?’

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Brookmeyer [1] is right to attempt the important task of reviewing and contrasting different approaches to biomarker-based HIV incidence estimates. The two ‘results’ highlighted in his abstract are as follows:

1. ‘The McDougal adjustment has no net effect on the estimate of HIV incidence because false positives exactly counterbalance false negatives’.
2. ‘The Hargrove adjustment has a mathematical error that can cause significant underestimation of HIV incidence rates’.

These findings appear to undermine the progress made in explaining why earlier BED assay-based methods have tended to overestimate incidence. However, both of Brookmeyer’s results are incorrect. Given the evidence for subpopulations who fail to progress out of the biomarker-defined ‘recent’ category (so-called assay nonprogressors), ‘adjustment’ is indeed necessary.

Brookmeyer outlines a conception of incidence estimation requiring demographic and epidemic equilibrium conditions over the past M years, in which M is the maximum time an individual remains classified ‘recent’ by the biomarker. He then claims that M is 3 years for the BED assay, thus excluding the possibility of assay nonprogressors. This seems hard to sustain in light of various data of which we are aware [2–4]. Hargrove *et al.* [3] provide data on postpartum mothers indicating that 5.2% of those surveyed remain persistently classified as ‘recent’ by the BED assay. McDougal *et al.* [2] infer from their data that an individual has a 5.6% probability (reported as a long-term specificity $\rho_2 = 0.994$) of testing below BED threshold, if infected longer than twice the mean window period of the assay. Under the *assumption* of no assay nonprogressors, Brookmeyer presents an argument to demonstrate that no ‘adjustment’ is required. His first result (point one above) is therefore inappropriate, as it depends on an assumption that is inconsistent with the data-driven findings in the publications he critiques.

Brookmeyer reports a numerical simulation in which the Hargrove estimator (using $\varepsilon = 0.052 = 1 - \rho_2$) apparently produces egregious underestimates of incidence, possibly even negative values. The cause of the underestimate is inconsistent calibration. The simulated epidemic has no assay nonprogressors, but he uses Hargrove's 'adjusted' estimator that assumes them to be 5.2% of the population. Although it is not reported, a near identical underestimate arises with the McDougal formula (when, equivalently $\rho_2 = 0.948$ is used). The bias merely reflects that the incidence estimators are unavoidably very sensitive to the calibration of ρ_2 , a very important and usually neglected point [4]. Conversely, if one samples or simulates a population in which there is a subpopulation of assay nonprogressors, then 'unadjusted' estimators are well known to overestimate incidence because a disproportionate number of 'false recent' classifications accumulate in the population. In this situation, the McDougal and Hargrove estimators, when appropriately calibrated, yield results with modest bias, dominated by counting error for reasonable sample sizes [3,4]. We provide an analytical closed-form demonstration of inherent bias in each of these methods [5]. Brookmeyer's other result (point two above), thus incorrectly attributes substantial bias exclusively to the Hargrove estimator when in fact both the McDougal and Hargrove estimators exhibit similar bias, which results from Brookmeyer's inconsistent calibration of the estimator.

As we have shown elsewhere [5,6], it is possible to simplify the McDougal framework, under its own assumptions, but not as Hargrove or Brookmeyer suggest. Detailed analysis reveals an identity relating the sensitivity and specificity parameters, leading to a simpler estimator that is easier to calibrate. We have also derived a formally rigorous framework for biomarker-based incidence estimation that specifically accounts for assay nonprogressors [7], and can also account for assay regressors under suitable calibration [4]. This approach requires fewer assumptions and is less prone to bias than either the McDougal or Hargrove method.

Brookmeyer notes the unsatisfactory correspondence between published biomarker-based incidence estimates and estimates based on prospective follow-up. His discussion of possible sources of error focuses on sampling bias and imperfect mean window period estimation. Although these issues are important, he proposes no way of dealing with assay nonprogressors. In his conclusion, Brookmeyer remarks that 'if, however, a proportion of HIV-positive persons are identified who remain in the window period indefinitely, then an adjustment would be necessary'. This does little to soften his strong statements, which undermine prior work addressing the issue of nonprogressors that has helped us move beyond the naive estimators.

Using data from cross-sectional surveys to estimate incidence will remain an attractive approach, but it requires the use of a robust estimator for which the correct applicable calibrations have been performed. In particular, accurate calibration of long-term specificity is of vital importance to correctly account for biomarker misclassification.

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