the evidence base for providing PrEP to sub-Saharan African migrants and other migrant and ethnic minority communities would further reinforce existing health disparities. Given the recent EMA approval, this call to rethink the European PrEP research agenda could not be more timely.

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HIV elimination and population viral load

WHO and UNAIDS have recommended treatment as prevention for the global elimination of HIV. Treatment suppresses an individuals’ viral load, making them less infectious. The higher the coverage of treatment, the lower the viral load in the population, and the lower the incidence of new infections. Incidence is very difficult to measure directly as it requires frequent testing of the entire population. Therefore population viral load, which can be used as an indirect measure of the effectiveness of treatment as prevention, has been proposed as a proxy for incidence. Population viral load is the average (mean or median) viral load, calculated from the distribution of viral loads in diagnosed and undiagnosed individuals. To date, only one HIV epidemic has been shown to be close to elimination: the Danish HIV epidemic in men who have sex with men (MSM).

HIV incidence in Danish MSM began to decrease soon after the introduction of effective therapies in 1996; by 2013, incidence was close to the WHO elimination threshold of one new HIV infection per 1000 individuals per year. Here we show how the population viral load changed, from 1996 onwards, as coverage increased and incidence decreased.

We calculated the population viral load each year between 1996 and 2013. To make these calculations we determined the number of diagnosed and undiagnosed MSM who were living with HIV, and their viral loads. We used data from the Danish HIV Cohort Study (DHCS), an ongoing population-based study, to make these determinations for diagnosed individuals. Diagnosed individuals were either not yet on treatment, on treatment but not virally suppressed, or on treatment and virally suppressed (<200 copies per mL). For the population viral load calculation we used individuals’
viral load measurements if they were untreated, or on treatment but not virally suppressed. In the first 2 years of the study (1996 and 1997), we used a value of 199 copies per mL for virally suppressed individuals. For virally suppressed individuals from 1998 onwards (as the test sensitivity had increased), we used the exact viral load measurement for individuals with a viral load between 200 and 20 copies per mL; we used a value of 19 copies per mL for individuals with a viral load below 20 copies per mL.

To specify the number of undiagnosed individuals, we used CD4-count stratified estimates from our previous analysis of the DHCS data. We assigned viral loads to these undiagnosed individuals using a bootstrap sample of CD4-count stratified viral load data from 1059 treatment-naive diagnosed individuals who participated in the study (figure 1). Since very few individuals in the DHCS had recently been infected (and were therefore in the acute stage of infection), we sampled from a distribution that was based on other studies to assign viral loads to undiagnosed individuals who were in the acute stage. The viral load in the acute stage is a characteristic of the natural history of HIV infection; consequently, it is appropriate to use data from other studies to specify a range of values for the viral load in the acute stage. We note that the small sample of patients in the DHCS that are characterised as being in the acute stage of infection have viral loads that fall within the range of values from the studies that we used.

In 1996, when effective therapies were introduced, the mean population viral load was 116,100 copies per mL and the median was 28,171 copies per mL (figure 2). These data are right-skewed (ie, the mean is always substantially higher than the median). This implies that, every year, there were a few individuals with very high viral loads.

The mean and the median population viral loads provide different insights into the changes in the internal dynamics of the epidemic as it was driven to the brink of elimination (figure 2). The median population viral load decreased as the proportion of infected individuals who were on treatment and virally suppressed increased. The median fell below 200 copies per mL in 2007, reflecting the fact that just over 50% were virally suppressed. By 2013, the median had fallen below 20 copies per mL (the limit of detectability). The mean population viral load also declined; this reflects a decreasing number of undiagnosed individuals, as well as the fact that the distribution of their viral loads became more concentrated at lower values. In 2007 the mean population viral load was about 100,000 copies per mL; by 2013 it had fallen to about 35,000 copies per mL. We determined, by using a function that transforms viral load into transmission risk, that the average per act probability of transmitting HIV decreased from 0·0041 (in 2007) to 0·0027 (in 2013). Notably, neither measure of population viral load completely captures the risk of transmission, as they do not reflect potential changes in risk behaviour. There are also other
important issues that need to be considered when using population viral load as a measure of ongoing transmission.4

Our results show that as treatment coverage expands and the incidence of new infections decreases, the mean population viral load is a more useful measure of the effectiveness of treatment as prevention than the median. The median has little utility once more than 50% of HIV-infected individuals are virally suppressed. However the mean will always be useful, even when incidence is close to the WHO elimination threshold, as it provides a measure of the risk of ongoing transmission.

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