Title
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Journal
AIDS, 31(17)

ISSN
0269-9370

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Publication Date
2017-11-13

DOI
10.1097/qad.0000000000001638

Peer reviewed

The missing 27%

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VIEWPOINT

Though a wide body of observational and model-based evidence underscores the promise of *Universal Test and Treat* (UTT) to reduce population-level HIV incidence in high-burden areas of sub-Saharan Africa (SSA) [1, 2], the only cluster-randomized trial of UTT completed to date, ANRS 12249, did not show a significant reduction in incidence [3]. More UTT trials are currently underway, and some have already exceeded UNAIDS's 90-90-90 targets [4-6]. Still, even with high test and treat coverage, it is unknown whether ongoing trials will engage populations with the greatest potential for onward transmission to achieve the ambitious goal of reducing new HIV infections and AIDS-related mortality by 90% between 2010 and 2030 [7] . Ultimately, even strategies that successfully meet or exceed the 90-90-90 targets will leave up to 27% of people living with HIV/AIDS (PLWHA) virally non-suppressed. The epidemiological profile of the "missing 27%" – including their risk behavior, mobility, and network connectedness – is not well-understood and must be better characterized to fully evaluate the effectiveness of UTT.

Part of the uncertainty in UTT's effectiveness rests in the risk profile of PLWHA who fail to achieve viral suppression. Some mathematical modeling has provided optimistic projections for the population-level effect of UTT on the course of the HIV epidemic [8, 9], with the size of the effect depending on epidemiologic context [10]. These models, however, are subject to varying degrees of parametric uncertainty and often do not explore the possibility of transmission heterogeneity across the HIV cascade of care [11-15]. In contrast to common model-based assumptions, engagement in the cascade of care is not independent of transmission potential [16, 17], and there is some preliminary evidence that those missing from the care cascade may be the ones most likely to transmit HIV. In the cluster-randomized ANRS 12249 and HPTN 071 (PopART) trials, for example, those unlinked to care tended to be younger [18-20] and in less-stable relationships [18, 19]. In the SEARCH cluster-randomized test and treat study, viral suppression at 2-years post intervention was 2-fold lower among 15-24-year-old HIV positive individuals compared those over 44 years [6]. Age-disparities in viral suppression within UTT is concerning given that younger populations may play a larger role in transmission than previously thought [21]. Model-based estimates of UTT effectiveness have also yet to fully consider the effect of mobile populations – who are at high risk of HIV acquisition and transmission [22], and are among the most difficult to engage in the cascade of care [23] – on UTT. Mobile populations tend to be younger, more likely to be living with HIV, and more likely to engage in higher-risk sexual behavior. [24, 25][26]. Given the unique risk profile and lower propensity to engage in the cascade of care among mobile populations, there is a need to incorporate more complex dimensions of population mobility into existing models of population-level UTT effectiveness. Novel approaches that adapt prevention strategies and care programs specifically for mobile populations may be crucial to achieving the ambitious goal of UNAIDS to end AIDS as a public health threat by 2030.

Finally, considerable debate exists as to the frequency of HIV testing needed for a UTT scenario to dramatically reduce incidence. This debate is centered primarily around the contribution of early and acute HIV (EHI) infection to onward transmission [27, 28]. While some argue that EHI threatens the population-level effectiveness of UTT [13, 29], others assert that, despite elevated infectiousness of EHI [30], yearly UTT can theoretically lead to HIV elimination [27, 31]. Mathematical models of UTT on HIV transmission dyanamics, however, often rely on simplifying assumptions about sexual risk behavior in the period immediately following HIV infection; assuming, for example, that sexual contact rates remain constant from initial infection through the early infectious period [13]. In fact, the risk profile of newly infected individuals – most of whom are unaware of their HIV status – may differ substantially from those who have been infected for longer periods of time [32], and theoretical simulation studies demonstrate that heterogeneity in sexual contact rates over time can dramatically increase the fraction of secondary infections that occur during EHI [33, 34]. In this way, epidemics with similar basic reproductive numbers (R_0) can theoretically exhibit considerable variability in the proportion of secondary infections that occur

during EHI. Settings where a large fraction of secondary infections occur during EHI will present a serious challenge to the promise of UTT [35].

Efforts are currently underway to better characterize the epidemiologic profile of populations that contribute the most to secondary infections in high-burden settings of SSA [36]. More studies from SSA, however, are needed to improve our understanding of risk-heterogeneity and the propensity for onward transmission across the HIV care cascade. Further modeling studies are also needed to assess whether projected long-term incidence reductions from UTT are sensitive to parametric uncertainties around transmission heterogeneity across the cascade of care and the proportion of secondary cases linked to EHI. Such efforts will greatly enhance the lessons learned from the UTT trials.

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