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VIEWPOINT

The missing 27%

Adam Akullian[a], Anna Bershteyn[a], Britta Jewell[b] and Carol S. Camlin[c]

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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 the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90–90–90 targets [4,5]. 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 by 90% between 2010 and 2013 [6]. Ultimately, even strategies that successfully meet or exceed the 90–90–90 targets will leave up to 27% of people living with HIV/AIDS 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 people living with HIV/AIDS (PLWHA) who fail to achieve viral suppression. Mathematical modeling has provided optimistic projections for the population-level effect of UTT on the course of the HIV epidemic [7], with the size of the effect depending on epidemiologic context [8]. These models, however, are subject to varying degrees of parametric uncertainty and often rely on simplistic assumptions about transmission heterogeneity across the HIV cascade of care [7,9–11]. In contrast to common model-based assumptions, engagement in the cascade of care is not independent of transmission potential [12,13]. In the cluster-randomized ANRS 12249 and HIV Prevention Trials Network (HVTN) 071 Population Effects of Antiretroviral Therapy to reduce HIV Transmission (PopART) trials, for example, those unlinked to care tended to be younger [14–16] and in less-stable relationships [14,15]. In the Sustainable East Africa Research in Community Health (SEARCH) cluster-randomized test and treat study, viral suppression at 2-years post intervention was two-fold lower among 15–24-year-old HIV-positive individuals compared with those over 44 years [5]. Age disparities in viral suppression within UTT is concerning given that younger populations may play a larger role in transmission than previously thought [17]. Model-based estimates of UTT effectiveness have also yet to consider the effect of mobile populations – who are at high risk of HIV acquisition and transmission [18], and are among the most difficult to engage in the cascade of care [19] – 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 [20–22]. 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 for achieving the ambitious goal of UNAIDS to end the epidemic by 2030.

[a]Institute for Disease Modeling, Bellevue, Washington, [b]Division of Biostatistics, School of Public Health, University of California, Berkeley, and [c]Department of Obstetrics, Gynecology, and Reproductive Sciences, Department of Medicine, University of California, San Francisco, California, USA.

Correspondence to Adam Akullian, Institute for Disease Modeling, 3150 139th Ave SE, Bellevue, WA 98005, USA.

Tel: +1 425 495 8662; e-mail: aakullian@idmod.org

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Finally, considerable debate exists as to the frequency of HIV testing needed for a UTT scenario to dramatically reduce the magnitude of the epidemic. This debate is centered primarily around the contribution of early and acute HIV (EHI) infection to onward transmission [23,24]. Although some argue that EHI threatens the population-level effectiveness of UTT [10,25], others assert that, despite elevated infectiousness of EHI [26], yearly UTT can theoretically lead to elimination [23,27]. Mathematical models of UTT on HIV transmission dynamics, however, have often relied 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 [10]. In fact, the risk profile of newly infected individuals – most of whom are unaware of their HIV status – differs substantially from those who have been infected for longer periods of time [28], 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 [29,30]. In this way, epidemics with similar basic reproductive numbers (R_0) can theoretically exhibit considerable variability in the proportion of secondary transmissions that occur during EHI. Settings where EHIs account for a large fraction of secondary infections may present a serious challenge to the promise of UTT [31].

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 [32]. More studies from SSA, however, are needed to fill empirical gaps in our understanding of the heterogeneity in sexual risk behaviors and the propensity of HIV 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 both transmission heterogeneity across the cascade of care and the proportion of secondary cases linked to EHI. Until these efforts are undertaken, our ability to evaluate and learn from early failures of UTT – as well as the reasons for potential successes – will be limited.

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Conflicts of interest

There are no conflicts of interest.

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