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The Next Generation of Research on HIV Adherence Interventions: No Time to Wait

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The Next Generation of Research on HIV Adherence Interventions: No Time to Wait Two decades since the discovery of life-saving antiretroviral therapy (ART) for HIV, adherence remains the primary obstacle to optimal outcomes among those engaged in treatment.[1] Despite the increased availability and affordability of potent once-daily regimens worldwide, the UNAIDS goal of 90% viral suppression eludes us.[2,3]

Dedicated funding has generated a wave of rigorous research on developing and evaluating interventions to promote ART adherence in both high- and low-resource settings.[4,5] Indeed, the CDC research synthesis project[6] has identified 13 interventions meeting "Good-evidence" criteria.[7,8]

The *Lancet Infectious Diseases* study by de Bruin and colleagues[9] is an outstanding addition to the adherence intervention compendium. In a multi-center randomized controlled trial, they evaluated a nurse-based counseling intervention (AIMS) involving promotion of self-management guided by review of electronically collected medication adherence data. AIMS was developed through iterative formative work which led to a feasible and acceptable intervention strategy demonstrating an impact on adherence behaviors. In this 15-month effectiveness study with 21 nurse providers across 7 clinics in the Netherlands, treatment arm participants demonstrated significantly superior HIV outcomes compared to those in the control arm. Moreover, a cost-effectiveness analysis suggested that AIMS saves society €592 while adding 0.034 quality-adjusted life years per patient.

The investigators' use of a pragmatic, effectiveness-oriented approach is particularly welcome. By testing interventions under conditions approaching the real world, sampling heterogeneous patient populations, and using routine clinical settings, effectiveness research enhances the likelihood that intervention effects will be sustained through scale-up. AIMS requires no additional or greatly lengthened clinic visits, extensive provider training, ongoing supervision, or patient incentives. Notably, the lack of variability in intervention effect by ethnicity, treatment experience, or individual nurse interventionist suggests the

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results may generalize beyond the study context. Despite some minor methodological limitations (e.g., the lack of analyzable ART adherence data), AIMS merits the national roll-out in progress. Indeed, Dutch clinics lacking the considerable adherence support available at the control arm sites may experience effects surpassing those observed in the trial.

Further dissemination and implementation science (DIS) research will be essential to ensure widespread adoption of the AIMS intervention, especially in resource-constrained settings. Feasibility and cost must be determined across a range of health systems. Provider training, though brief, might nonetheless be burdensome in settings with high staff turnover. A task sharing approach, using a cadre of adherence specialists with less training,[10] might prove more feasible. Additionally, acceptability of electronic drug monitoring (EDM) may be a significant barrier to implementation. Almost 60% of potential participants refused to participate in the AIMS trial, commonly citing the bulky, non-discrete EDM bottles with only a single compartment, alongside fear of disrupting their daily medication-taking routines. EDM also can be prohibitively costly. Capitalizing on advances in EDM technologies, novel mHealth devices, and other adherence assessment strategies (e.g., pharmacy refills) might improve acceptability, feasibility, and affordability. Moreover, although EDM data are integrated into most key intervention components, we do not know whether the assessment of daily adherence patterns (as with EDM) and the joint review of printed output in intervention sessions are critical to intervention effects. Future work might involve dismantling AIMS to elucidate its most powerful components, along with analyses of potential mediating pathways.

The AIMS trial paves the way for the next generation of ART adherence research, pushing the field toward the DIS research necessary for wider scale-up. Although emerging strategies to improve ART adherence - like mHealth or those targeting key populations – will still require conventional efficacy testing, approaches with empirical support sitting idly on the shelf are prime targets for broader effectiveness trials with economic components such as de Bruin’s. These should address how best to increase intervention acceptability, monitor fidelity, improve sustainability, facilitate dissemination, and achieve equitable service delivery across a range of treatment settings. Rigorous work in this area will require expertise in DIS theories, methods, and analytic approaches.

This next generation of ART adherence research must proceed expeditiously. AIMS was originally developed in 2003, meaning its lag from innovation to implementation approaches the average - yet unacceptable – 17-year cycle typical of health research translation.[11] The 37 million persons living with HIV/AIDS worldwide cannot wait.

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