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Lifetime HIV Antiretroviral Therapy Adherence Intervention:

Timing Is Everything

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Modern, potent antiretroviral therapy regimens can suppress human immunodeficiency virus (HIV) replication indefinitely. For those who have access to these drugs and who are able to adhere on a daily basis to these drugs, life expectancy now approaches that of individuals without HIV infection, particularly if they start therapy early.^{1,2} Full lifetime viral suppression offers the potentially transformative public health benefit of reducing transmission leading to a decline in number of new HIV infections.³

For many patients, however, adequate adherence to sustain viral suppression over a lifetime remains a major challenge. Antiretroviral adherence declines over time.^{4–6} Even people with typically excellent adherence will experience treatment interruptions owing to inevitable disruptions in daily routine, relapse of substance use or mental illness, or simple pill fatigue. Interruptions of several days or more put patients at risk for virologic failure.^{7,8} As such, adherence support may be necessary for many, if not most, people at some time in the course of life-long treatment in order to achieve the full individual and public health impact of antiretroviral therapy.

Providing adherence support over a lifetime of anti-retroviral therapy creates 2 major conundrums. First, most adherence interventions are time limited, and benefits do not typically last much beyond the cessation of the intervention.⁹ Second, we don't know when individuals most need adherence support during a lifetime of treatment. Continuous, lifelong adherence support is neither necessary nor possible.

In this issue of the journal, Gross et al¹⁰ make significant progress toward a model of effective long-term adherence support. In a US population, they randomized subjects with plasma HIV-1 RNA levels higher than 1000 copies/mL who were initiating or changing therapy to an intervention of Managed Problem Solving (MAPS) vs usual care. Managed Problem Solving consisted of 4 in-person and 12 telephone-based meetings with a trained

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interventionist, followed by monthly follow-up calls for a year. In the primary intention-to-treat analyses, the odds ratio of being in a higher adherence category was 1.78 (95% CI, 1.07-2.96) times greater for MAPS than usual care, and the odds of having an undetectable HIV RNA level were 1.48 (95% CI, 0.94-2.31) times greater for MAPS than usual care. The effect was sustained for 12 months, involved minimal interaction with the study participants, and did not deteriorate over time. While this intervention achieved a durable behavioral and biologic effect, calling every HIV-infected person on treatment every month of their life may not be feasible or necessary. We believe that to maximize the benefit of the findings reported herein, individuals who might benefit from MAPS need to be offered this intervention in connection with adherence lapses. One such approach is to use life-long, real-time adherence monitoring.

Real-time adherence monitoring involves electronic pill containers that transmit a time and date stamp with an anonymous patient identifier to a central server through mobile networks every time the pill container is opened. Monitoring detects missed doses in real time and thus provides a means to link MAPS (or other interventions) to an individual before treatment failure occurs. Support can be provided not on a fixed monthly interval, as in the study by Gross et al,¹⁰ but rather only when needed in the midst of an adherence lapse. “Just-in-time” adherence support can be delivered by text message, live counseling over the telephone, or in person, depending on the duration and cause of the adherence lapse. While the cost of electronic monitors is not insignificant, on a large scale, real-time monitoring and adherence-driven support could be provided at costs comparable with those of current laboratory monitoring for HIV. This approach transforms HIV care from largely responding, to proactively preventing virologic failure in real time. It is potentially cost-effective when considering the savings achieved through long-term virologic suppression, which prevents need for resistance testing, avoids the use of more expensive second-line regimens, and avoids devoting substantial resources to managing the complications of disease progression. Initial studies have shown real-time adherence monitoring to be feasible even in areas with limited infrastructure.¹¹ Moving forward, research is needed to establish effectiveness and ultimately scalability outside the research context.

The introduction of combination antiretroviral therapy transformed HIV from a terminal to a chronic disease in the late 1990s. Advances in simpler, more potent therapy transformed treatment from success in some to success in most in the 2000s. Advances in just-in-time adherence monitoring and support delivered when and where it is needed may transform treatment from success measured over years to success measured over a lifetime.

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