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Words Matter: Discussing Research Towards an HIV Cure in Research and Clinical Contexts

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While still aspirational, the concept of curing HIV infection is gathering momentum as basic science concepts move into clinical research studies. The International AIDS Society has led strong advocacy efforts, paving the way for “HIV cure” to transition from being a four-letter word to being a strategic research priority of all the main HIV funding agencies worldwide, including the United States National Institutes of Health. This research excitement will gradually return to the clinic when patients pose questions to their HIV clinicians about how to interpret the meaning of HIV cure research. But HIV clinical cure research today has only peripheral relevance to the clinical management of HIV-infected individuals and simply using the term “cure” with patients in the clinic may invite more questions than it answers. As language wields power and HIV cure research is still early, now is a key time to clarify the nomenclature in research and clinical contexts. We first examine the concept of “cure” and then review three conceptual frameworks (sterilizing/functional cure, sustained virological response (SVR), clinical remission) for explaining the meaning of possible HIV cure to HIV-infected patients. The SVR concept may be useful in clinical research settings, but the concept of clinical remission has greater explanatory power, especially outside of research settings.

With essentially all diseases, the term “cure” implies that all evidence of the disease has been eliminated and the individual has no chance of a recurrence. Given this high burden of diagnostic evidence and the high expectations it reproduces, the term “cure” is rarely used in the clinic. Most common infections are treated (e.g., bacterial infections) or resolved (e.g., viral infections). Meanwhile, in cancer clinics, physicians hesitate to use the word “cure” at least until sufficient time has passed after treatment to ensure that recurrence is highly unlikely. The difficult judgment about recurrence is contingent on the passage of time and

testing. Decades of clinical experience provide physicians with a framework for prognosticating about the likelihood of recurrence. This is especially important in the cancer field in which some cancers recur many years after all evidence of cancer has resolved. Testing provides further data in which to inform patients about the probability of recurrence. Yet our experience with possible HIV cures is new and tools to detect and measure latently infected cells must be improved. We need to carefully examine the uncertainties and nomenclature of possible HIV cures.

First, the concepts of sterilizing and functional cures provide a scientific foundation and likely catalyze hope, but ultimately have marginal relevance or explanatory power in the context of HIV-infected individuals. The International AIDS Society's (IAS) Scientific Working Group, "Towards an HIV Cure" proposed a technical differentiation between a sterilizing and functional cure.¹ A sterilizing cure is the elimination of all cells that could ever produce infectious HIV, while a functional cure is a less clearly defined term. Some have explained the latter as "the generation of effective host immunity to HIV that would result in lifelong control of the virus in the absence of therapy, despite not achieving the complete eradication of HIV."¹ The concept of functional cure has also been said to promise a stable health prognosis, the assurance of not being able to infect others, and have children without fear of HIV transmission. While sterilizing and functional cure concepts have helped galvanize advocacy and generated new hope for a cure, accurately defining either of these categories has proved challenging. The detection of HIV DNA alongside the absence of replication-competent, infectious HIV in both the Berlin patient² and the Mississippi baby³ illustrate that while these patients appear to represent a sterilizing cure, definitively proving the absence of infectious virus is challenging. Using the functional cure concept may undermine the vigilance necessary to follow these patients long-term in clinical settings. Few other diseases have functional cures⁴ and this further complicates explaining a functional cure to patients.

Second, the SVR concept balances the science with appropriate clinical uncertainty, but would also be unfamiliar to many HIV-infected individuals. SVR refers to lack of detectable RNA in the serum of individuals with hepatitis C virus (HCV) at six months after stopping therapy.⁵ This definition directly corresponds to a measurable unit in the blood at a specific time point, appealing to scientists and many physicians. Although the SVR concept comes close to complete cure, there is still a subset of HCV-infected patients who achieve SVR but then display persistent hepatic inflammation and develop cirrhosis.⁶ The Forum for Collaborative HIV Research has proposed using the term "sustained virological suppression off therapy" (SVOT), analogous to the SVR concept. This term would likely be useful in early clinical research settings, but would have less utility as more individuals enter clinical research studies.

Finally, the concept of clinical remission denotes improvement with some uncertainty and is already well-entrenched in medical settings. The term's medical use stretches back to the 15th century and means, "lessening the severity of a disease or symptom for a period".⁷ The concept is frequently used in the cancer clinic and describes the absence of disease activity in the setting of chronic cancer. Remission is used to describe scenarios in which cancer is curable (e.g., acute lymphoblastic leukemia), incurable (e.g., metastatic melanoma), or

unknown (e.g., carcinoma of unknown primary). Although widely used in cancer clinical discussions, clinical remission is also used to describe a wide range of other non-cancer chronic diseases. The remission concept clearly denotes improvement, but also underscores vigilance and uncertainty that require the need for careful follow-up. In addition, the remission concept can be further subdivided into partial and complete remissions, a helpful designation given the likely stepwise progression towards an HIV cure. Although the remission concept may be less familiar in low-income country settings, it would be largely recognizable to HIV-infected individuals in a wide range of other settings. The remission concept has been used by leadership at the National Institute for Health's National Institute of Allergy and Infectious Diseases⁸ and the International AIDS Society.⁹ The concept of "HIV remission" may be particularly useful as more HIV-infected individuals enter clinical trials and physicians are discussing this concept outside of research settings.

Embracing the concept of clinical remission does not mean that we have abandoned hope of finding therapies that could create a sterilizing cure, nor are we advocating for scientific research and advocacy to halt the aspirational (*towards* an HIV cure) language that has ignited a new subfield of HIV research. Clinical discussions between physicians and patients require honesty about the uncertainty in this undertaking. Such careful communication may present waves of hope, misperception, and disappointment among HIV-infected individuals and the health professionals who serve them. Should effective HIV cures be developed, the downstream effects on health and well-being, risk of onward transmission, risk of re-acquisition, and social stigma are unclear. Furthermore, these larger biological and social questions will not be addressed by nomenclature. But nomenclature critically sets the bar for expectations as research advances and clinicians increasingly discuss cure research with their HIV patients. While only two individuals in all of history appear to be cured of HIV infection, the concept of remission is both easier to explain and more consistent with the state of the science. We owe it to our HIV patients to use caution and consider the conceptual framework of HIV remission.

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