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Viewpoint

Re-examining the HIV 'functional cure' oxymoron: Time for precise terminology?

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ABSTRACT

For over a decade, the binary concepts of 'sterilizing' *versus* 'functional' cure have provided an organizing framework for the field of HIV cure-related research. In this article, we examine how the expression 'functional cure' is employed within the field, published literature, and community understanding of HIV cure research. In our synthesis of the different meanings attributed to 'functional cure' within contemporary biomedical discourse, we argue that employing the 'functional cure' terminology poses a series of problems. The expression itself is contradictory and inconsistently used across a wide array of HIV cure research initiatives. Further, the meaning and acceptability of 'functional cure' within communities of people living with and affected by HIV is highly variable. After drawing lessons from other fields, such as cancer and infectious hepatitis cure research, we summarize our considerations and propose alternative language that may more aptly describe the scientific objectives in question. We call for closer attention to language used to describe HIV cure-related research, and for continued, significant, and strategic engagement to ensure acceptable and more precise terminology.

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Introduction

Central to the immune system's defense against infectious pathogens is its ability to generate an effective, multimodal response capable of neutralizing a threat as well as mobilizing quickly if the pathogen is encountered again.[1] HIV subverts this response by integrating within the host cells' DNA to establish a reservoir, exploiting the immunologic processes that typically work against pathogens, and causing dysregulation within the immune system.[2] While antiretroviral therapy (ART) is able to suppress plasma levels of HIV, prevent progressive immunodeficiency, and restore health, it is unable to completely clear infection or eliminate the virus reservoir. This inability to eliminate the latent proviral reservoir remains the main barrier to curing HIV infection.[3]

For over a decade, the binary concepts of 'sterilizing' *versus* 'functional' cure have provided an organizing framework for the field of HIV cure-related research. A 'sterilizing cure'–also conceptualized as a 'complete cure', 'classic cure' 'eliminating cure' or 'eradicating cure'–would result in complete elimination of HIV from the body, while a 'functional cure' would induce ART-free durable control of HIV infection. Many scientists believe that a functional cure may be more easily achievable and scalable than a 'classic cure.' Further, some of the authors of this article advocate against using the term sterilizing to describe a scenario of HIV cure due to its association with disinfection, sterility, and forced sterilization efforts.[4,5]

As of September 2020, there have been over 250 active or completed HIV cure-related studies around the world.[6] The biomedical HIV cure-related research landscape is complex, with multiple intersecting modalities, many of which are aimed at depleting HIV reservoirs and modifying the immune response to induce long-term ART-free HIV control.[7] Interventional HIV cure-related studies include those investigating early ART in hyperacute or acute infection, chemotherapy and transplantation, latency reversing agents, antibody-based therapeutics, immune modulation, therapeutic vaccines, cell therapies, and gene therapies–used alone or in combination in many instances.[8] Measurement of the outcomes of these experimental interventions poses a challenge, as analytical treatment interruptions (ATIs)–in which participants pause ART–will continue to be necessary until a biomarker able to predict post-treatment control (PTC) or the optimal viral rebound necessary to boost the immune system is eventually discovered.[9]

In this article, we review the many ways in which the description 'functional cure' is employed within HIV cure-related research trials, published literature, and community understanding of HIV cure research. In our review of the different meanings attributed to 'functional cure' within contemporary biomedical discourse, we argue that employing this terminology poses a series of problems. The expression itself is contradictory and is inconsistently used across a wide array of HIV cure-related research initiatives. Further, the meaning and acceptability of 'functional cure' within communities of people living with HIV (PLWHIV) or affected by HIV is highly variable. After drawing on lessons from other fields, such as cancer and infectious hepatitis cure research, we summarize our considerations and propose alternative language that may more aptly describe the scientific objectives of HIV cure-related research efforts. We call for closer attention to the language used to describe HIV cure-related research, and for continued, significant, and strategic engagement to ensure acceptable and accurate terminology among key stakeholders, including researchers, health care providers, and PLWHIV.

Discussion

Terminology in HIV cure-related research

A number of articles have scrutinized the language used to describe HIV cure-related research.[4,10–15] None, however, has explicitly reviewed the 'functional cure' concept. For over a decade, the dichotomous 'sterilizing' *versus* 'functional' cure concepts have provided the predominant organizing framework for the global scientific HIV cure-related research agenda.[16] On the one hand, 'sterilizing cure' refers to complete elimination of all HIV-infected cells from the body (i.e. pathogen-free or infectious disease model).[4,17–19] Depending on the modality used to confer cure, a person may or may not become protected against HIV re-infection. Diseases such as syphilis, malaria, tuberculosis (TB), and now hepatitis C (HCV) provide examples of diseases that can be completely cleared from the body (though re-infection is still possible). Another example would be a simple bacterial infection that can be eliminated with a finite course of antibiotics. On the other hand, 'functional cure' has been used most frequently to refer to long-term control of HIV without the need for ART, similar to cancer remission models. Long-term control of HIV without ART signifies that one's immune system is capable of controlling HIV in the absence of regular administration of anti-HIV agents; however, a viral reservoir remains present. Here, hepatitis B (HBV) or herpes simplex virus (HSV) represent useful analogies for 'functional cure' or durable suppression (discussed further below).

The adjective 'functional' in 'functional medicine' refers to strengthening normal health body processes, such as those aimed at regulating or restoring function.[20] If applied to HIV, this would mean restoring the immune system's ability to combat infection and facilitating long-term control. In the general lexicon, a 'cure' suggests that any evidence of disease has been removed, or that the patient has negligible or no chance of disease recurrence.[11] 'Functional cure' in HIV-related nomenclature contains a conflicting message because it attempts to embody both the infectious disease ('virus-free') and the oncology ('remission') models. When used in combination, we argue the terms 'functional' *and* 'cure' create a contradictory figure of speech. The logical inconsistencies inherent in the terminology 'functional cure' can lead to confusion and misunderstanding about the nature and aims of investigational HIV cure-related research strategies.

'Functional cure' concept

The 'functional cure' concept first appeared in the lexicon in 2001, when HIV treatment activist Martin Delaney proposed a new vision for an HIV 'cure'.[21] Delaney's vision was as follows: "*[i]nstead of equating cure with an unobtainable state of HIV-free perfection, we should redefine it as a state that allows you to live out a normal lifespan without day-in, day-out drugs.*"[21] Ten years later, in 2011, the concept was applied to the state of elite control of HIV: biomedical scientists described how elite controllers (ECs) represented prototypes for a 'functional cure'.[22] The EC phenomenon was also referred to as 'natural suppression' or 'durable HIV control' and was found to depend on host genetic factors facilitating virologic control in the plasma compartment, in part through robust cell-mediated immunity.[22] Elite control, however, was determined not to be without consequences. These included evidence of persistent viral replication, chronic inflammation, immune dysfunction, and comorbid disease.[23–30] As described by Autran and colleagues a decade ago, only a small proportion of ECs– at the time called long-term non-progressors (LTNPs)–were thought to be truly 'functionally cured' due to "long-term virus undetectability and stable immune competence."[22] More recently, the even rarer concept of "exceptional" control has emerged as having the potential to inform HIV cure-related research, but many of the consequences seen in exceptional ECs have yet to be explored in this phenotype.[31–33]

HIV cure-related research: ART-free HIV control versus elimination

In the last decade, the field of HIV cure-related research has flourished with the intent to develop interventions that induce a state of sustained ART-free HIV control or elimination. Several strategies have been described. Latency-reversing agents ('kick and clear') refers to strategies in which HIV quiescence is reversed, the reservoir becomes vulnerable to immune surveillance, and HIV-infected cells are ultimately cleared. Permanent silencing ('block and lock') is a strategy in which the virus is forced into a state of deep latency, in which it can no longer

actively replicate and essentially becomes inert. A more recent strategy is the concept of 'reduce and control', in which the viral reservoir becomes diminished in size and is subsequently held at bay. In the HIV-free or infectious disease ('eradication') model, the virus and its reservoir would be completely eliminated.[12] While latency-reversing agents would be an example of eradicative strategy, permanent silencing would be an example of a functional strategy, and 'reduce and control' an example of a combined strategy.[8,19]

Three individuals are believed to have achieved a state of 'complete cure' of HIV infection following biomedical intervention. The first patient, Timothy Ray Brown–otherwise known as the Berlin patient–went through a process of seroreversion after undergoing hematopoietic stem cell transplantation (HSCT) from a donor homozygous for the CCR5 Δ32 mutation to treat acute myeloid leukemia (AML).[34] Mr. Brown remained without evidence of HIV infection thirteen years following his transplant and discontinuation of ART.[35] The second patient, Adam Castillejo–known as the London patient[36]–received a single HSCT without irradiation and with reduced intensity conditioning to treat Hodgkin lymphoma.[37,38] The first report of Mr. Castillejo's case in 2019 described him as being in a state of 'long-term remission' 18 months post-ATI initiation.[37] Authors of the initial 2019 report were extremely cautious not to employ "cure" terminology, stating: '*it is premature to conclude that this patient has been cured*'.[37] The second report in 2020 confirmed Mr. Castillejo's cure 30 months after interrupting ART.[38] With more extensive sampling of HIV reservoir sites and no evidence of replication-competent HIV, researchers concluded that Mr. Castillejo had indeed been 'cured'.[38] His case illustrates how the 'cure' terminology represents a temporal concept in that only time can tell if someone is actually cured. A third person, known only as the Düsseldorf patient, is also possibly cured of HIV infection. Following intensive HSCT to treat AML, no viral rebound was observed 83 months post-transplant and 15 months post ATI.[39]

There are similarly emblematic cases of adult individuals who have achieved a state of ART-free durable HIV suppression without eradicative cure. These include persons in the VISCONTI cohort (Viro-Immunologic Sustained CONtrol after Treatment Interruption), who are called 'post-treatment controllers' (PTC). Post-treatment controllers are PLWHIV who started ART within weeks of HIV acquisition and stayed on ART for a mean of 4 years before stopping therapy.[40] These individuals achieved viral control for a median of 7 years–despite lacking the protective HLA-B-57 and HLA-B-27 alleles.[8] Scientists believe that natural killer (NK) cells may be responsible for the VISCONTI participants achieving long-term HIV control. Additionally, in the United States, the CHAMP (Control of HIV after Antiretroviral Medication Pause) study identified 67 post-treatment controllers out of 700 ATI participants across 14 studies–38 of whom initiated ART during early HIV infection and 25 of whom were treated during chronic HIV infection.[41] Of all post-treatment controllers, 55% were able to maintain HIV control off ART for 2 years, with approximately 20% maintaining durable suppression for ≥5 years.[41] Post-treatment control frequency was estimated at 13% in early-treated individuals versus 4% in chronically-treated patients ($p < 0.001$).[41] Furthermore, PTCs have also been described in the pediatric HIV cure-related research literature.[42]

How cure is described in other fields

In seeking to define 'cure' in the HIV context, it proves prudent to examine the precedents set in other fields by posing the question, "*How have other fields dealt with the conundrum of describing a 'cure' when it is only temporal, transient, or partial?*" In a 2015 paper on 'The Ethics of Talking about HIV Cure,' Rennie and colleagues made a distinction between the *absolute* and *pathogen-free* notion of cure on the one hand, compared with the *chronic disease model* emphasizing reduced chance of resurgence on the other.[10] The authors explored how this entrenched dichotomy reflected *categorical* (definitive) conceptions of cure versus *statistical* (probabilistic) likelihoods of recurrence.[10] The cancer remission analogy has been of particular importance in this discussion. Much like cancer, HIV is a residual disease. In both conditions, cure is limited by the persistence of rare cells.[43] The U.S. National Institutes of Health (NIH) uses the expression 'sustained ART-free HIV *remission*' to describe alternatives to 'classic cure'.[44] Tucker and colleagues argued that the concept of clinical remission retains significant explanatory power because it denotes "improvement with some uncertainty" and the need for sustained vigilance and careful monitoring.[11]

The fundamental difficulty in determining when, after a curative intervention, improvements in health become clinically significant and result in a state of 'functional cure' has been noted in the cancer field.[10] For example, as with *Kaposi sarcoma* or melanoma, the pathway to establishing a 'cure' involves measurement of tumors to determine the effect of interventions, with designations of no response, partial response, complete response, or progressive disease. In the HIV field, clinical improvements (e.g., sustained undetectable viral load, maintenance of the $CD4^+$ T cell count, lack of disease progression, no transmission risk, and no necessity for ART) would signal possible HIV 'remission'.[10] A larger question is whether there are inflammatory consequences–like those seen in many ECs off ART–that persist despite viral control. As several scholars have inquired in the past, *how will we know* when PWLHIV are decidedly 'functionally cured,' and *what is the appropriate timeframe*? [10,19,45]Undoubtedly, sustained clinical monitoring and regular testing of plasma HIV viral load will be required for an accepted period of time within the field. Zerbato and colleagues contend that as more PLWHIV participate in HIV cure-related research and statistical power increases, aggregate data will allow scientists to derive more precise predictions of possible sudden rebounds in HIV replication.[45] The search for such biomarkers is an area of active investigation. In turn, these practices, data, and concepts will help inform definitions surrounding possible clinical remissions or cures.

When introduced to communities of PLWHIV, however, the remission analogy appears problematic. For example, Sylla and colleagues, in conducting focus groups at HIV cure clinical research sites in the United States, reported that PLWHIV viewed remission as entirely inconsistent with a 'cure'.[46] For several participants, remission was reminiscent of how people eventually relapsed, only for cancer to return and become vengefully fatal: "*when it came back it just came as a vengeance*".[46] In these focus groups, PLWHIV ascribed negative feelings to the "remission" concept due to its association with the possibility of sudden recurrence.[46] Similarly, Power and colleagues showed how PLWHIV in Australia did not consider 'remission' as a state of 'cure' because it provided no relief from the anxiety associated with the possibility of HIV transmission during unsuspected relapses in viremia.[47,48] PLWHIV are *the* main stakeholders in HIV cure-related research. For those currently undetectable on ART, the idea of remission may seem to be less desirable than their current state.

Time elapsed and likelihood of recurrence play a role in conceptualizations of remission. The oncology model has adopted the '5 years without recurrence' benchmark for remission for many cancers, based on years of observed data and statistical modeling that demonstrate a very low likelihood of recurrence.[10] Could HIV, as an infectious disease, adopt a similar definition? In a 2018 nationwide survey of 282 PLWHIV in the United States, we asked: '*After how many years of HIV control without treatment ('HIV remission') will we know that the patient is 'functionally cured'*?' We found important heterogeneity in perceptions of what 'HIV remission' meant for PLWHIV. Of all respondents, 11% responded 6 months or fewer. Other responses were as follows >6 months–1 year in 11%, >1–2 year(s) in 26%, >2–3 years in 9%, >3–5 years in 21%, >5 years in 15%, and 6% responded 'other'.[49] *How* would these views differ among biomedical HIV cure researchers, HIV care providers, and regulators? And *who* should decide what is the proper definition of remission in the HIV space?[10] In the absence of longitudinal data, as exist in oncology, it would be very difficult to determine a meaningful duration of ART-free virologic control that would indicate little likelihood of recurrence, could be declared a remission, and would respond to the

concerns of PLWHIV detailed below.

Another term sometimes used by the NIH to describe durable ART-free virologic control is 'durable virologic suppression'.[50] This term describes what is happening in the body and is devoid of the psychological meanings ascribed to such words as cure or remission. Similarly, borrowing from the infectious hepatitis field, the concept of 'sustained virologic response' (SVR) can provide insight.[11] In HCV research, SVR means a lack of detectable virus in the serum 12 months after therapy discontinuation.[11] Tucker and colleagues explained how SVR terminology, in balancing "the science with appropriate clinical uncertainty", may appeal to scientists and clinicians, while remaining unfamiliar to many PLWHIV.[11] One of the first SVR and structured treatment interruption studies in the HIV field was performed by Davey and colleagues in the late 1990s.[51] Of the 18 participants who interrupted ART, all experienced HIV viral load rebound, and only one experienced modest SVR–or delay in viral rebound for 7 weeks.[51] Since then, SVR was rebranded as 'virologic suppression off therapy' (VSOT) in the HIV cure-related research field and remains in use in the literature.[11]

While the HCV field focused on achieving SVR to advance therapeutic options, the HBV literature embraced the 'sterilizing' *versus* 'functional cure' terminology.[52] Revill and colleagues define an HBV cure as a "complete sterilizing cure with undetectable hepatitis B surface antigen (HBsAg) in serum and eradication of HBV DNA, including intrahepatic cccDNA and integrated HBV DNA."[52] In contrast, an HBV 'functional cure' represents a stable state post-therapy equated with "sustained undetectable HBsAg and HBV DNA in serum with or without seroconversion to HBV surface antibody (anti-HBs), with the persistence of low levels of intrahepatic cccDNA."[52] Functional HBV cure or clinical resolution occurs spontaneously in 90% of adult patients during the acute phase of infection.[53] HBV-associated liver disease can also be in remission.[52] In reviewing ethical issues associated with HBV cure research, however, Sugarman and colleagues described how the use of the word 'cure' can be misleading, giving participants a sense of certainty generated by the proposed HBV research, when in reality it may take years or even decades for a virological 'cure' to materialize.[53]

Similar to HBV infection, HSV is a persistent virus that establishes lifelong infection in humans. HSV lives in the dorsal root ganglia of the nerves that innervate the regions that were infected and can cause outbreaks in those regions by migrating down the nerves. HSV infection is characterized by intermittent periods of viral latency and reactivation. In HSV, the focus has been maintaining *suppression* to reduce frequency of recurrences and symptomatic outbreaks.

In the non-communicable disease (NCD) domain, the terms *management*–i.e., hypertension or heart disease management and *control* or diabetes control, have been widely used. Notably, new clinical trials are underway to find a 'functional cure' for diabetes.[54,55] Non-Western medicine encourages moving beyond purely biological notions of cure to consider and appreciate the more holistic psychological and social dimensions of healing.[10,56–60]

Community and patient perspectives should predominantly inform conceptions of cure. As with all types of biomedical research, individuals construct mental models and social meanings to make sense of biomedical science.[61,62] In the United States, social scientists found that PLWHIV have great distrust of any 'functional cure; ' they view this approach as unremarkable. To PLWHIV, 'functional cure' sounds like an expensive treatment option that may not guarantee viral suppression and may defeat the purpose of 'cure' research.[46] In a 2015 survey of 397 PLWHIV in the United States, 'cure' meant having HIV completely eliminated from the body (68%), no risk of transmitting HIV to others (68%), no more HIV treatment ever needed (64%), no risk of opportunistic infection (47%), no more HIV treatment needed now (40%), or negative HIV test (30%).[63] In a global context, Ma and colleagues found that PLWHIV had learned to coexist with HIV and adjusted well to a lifetime prospect of ART adherence.[58] When the lead author (KD) visited a research site in South Africa, the concept of 'post-treatment control' was preferred by a local community advisory group. The word 'cure' was strongly discouraged by local activists, since it could easily be conflated with 'false cures' that have a long and dangerous history in the country. In Zulu, the goal of post-treatment control research was reframed as "*cindezeleka kwegciwane ngaphandle kwemishanguzo*" (translation: "suppression of HIV without antiretrovirals (ARVs)") (personal communication). Although lengthy, this expression made the most sense to the local community.

One of the great contributions provided by social sciences studies in both resource-rich and resource-limited (often overlooked in cure-related research) settings is that both have revealed that PLWHIV would prefer to reserve the word 'cure' to denote complete elimination of HIV from the body.[46–49,57,58,64–66] For example the Sylla et al. study in the United States showed that participants were skeptical about the durability of a 'functional cure'.[46] The expression 'functional cure' was rendered less meaningful due to concerns related to associated medical complications and psychological distress (e.g., anxiety linked with sudden viral rebounds).[46] Some participants felt that current ART represents a 'functional cure' because it permits virus undetectability and inability to transmit virus as suggested by the strong evidence of Undetectable = Untransmittable (U = U).[46] Similarly, the Power et al. study in Australia found that 'functional cure' was viewed as an extension of HIV treatment, not a cure.[47] As mentioned above, a cure was likewise defined in social terms, such as relief from worry about the potential for onward HIV transmission.[47] The Ma et al. study in China found that participants did not understand the medical distinction between 'sterilizing' and 'functional' cures and had difficulty visualizing a 'functional cure'.[57] Finally, Moodley et al. writing in the South African context, issued a strong caution around attributing the word 'cure' to these 'functional' breakthroughs.[66] In South Africa, cure was often equated with the resolution of symptoms, rather than elimination of viral particles.[64] Very few people understood the notion of viral reservoirs.[65] More worrisome is the erroneous belief that those who have achieved an undetectable HIV status are 'cured' and no longer need to adhere to ART (personal communication).

Social meanings around biomedical research can evolve and be reconstructed,[61] as can behaviors with the emergence of new evidence and technologies. In the U = U era,[67] the notion of undetectability is reducing stigma for some communities–a major priority in HIV research. Becoming undetectable for HIV is a notable milestone in the therapeutic trajectory of PLWHIV, and their emergent personal, social, and sexual identities.[68–70] However, new research is urgently needed to better understand participants' perspectives related to the likelihood of becoming detectable for HIV during ATIs, the possibility of viral rebound occurring unexpectedly, and related stigma and psychological implications.[71,72] The ability to again transmit HIV is also an important factor to be investigated. An emerging consensus is that such viremia caused by ATIs might be important in allowing the reconfigured immune system to eventually attain control.[9]

On the other end of the spectrum in therapeutics, social sciences studies on long-acting ART formulations reveal how these options may blur the boundary of what it means for PWLHIV to be 'functionally cured' or 'in remission'.[73] In a survey of 282 PLWHIV in the United States, 42% were willing to switch from oral daily ART to long-acting ART injectables or implantables taken at 6-month intervals, compared to 24% who would switch to a hypothetical ART-free 'remission' strategy that would not require taking ART.[49] What is becoming clearer is the urgent need to better understand patient perspectives in the development of novel HIV therapeutics.[74] Biomedical HIV cure researchers will need to show how novel strategies provide clinical advantages over oral daily ART, long-acting ART, and other anti-viral options in development. It will also be critical to communicate these advances in a manner that is clear, consistent and meaningful to PLWHIV.

The complex landscape of HIV cure-related research

In addition to patient and community perspectives, it may be worth exploring the current scientific landscape of HIV cure-related research.

The Treatment Action Group (TAG) listing of HIV cure research trials reflects the diversity of approaches under investigation.[6] This continually expanding listing underscores the need for greater precision in language when describing HIV cure-related research approaches.[6] ART-free durable HIV suppression or control will likely not be monolithic. For example, ART-free HIV control could mean either: 1) long-term HIV control, but requiring intermittent or continual non-ART interventions, or 2) long-term HIV control without the need for further intervention.

In a 2019 scientific update to the community, the expression 'functional cure' was used to describe the first stage of a 'classic cure', meaning: 1) the first several months or years following an intervention, 2) without detectable HIV, and 3) with uncertainty whether someone is truly cured and whether the virus will rebound.[8] The paradigmatic examples here were the cases of the two Boston transplant patients who apparently experienced transient 'functional cure' before their virus rebounded.[75,76] In reviewing this categorization further, we believe the Boston patients, prior to HIV relapse, represented 'potential cures' instead of 'functional cures'.

To add to the confusion resulting from inconsistent and contradictory use of the term, both 'sterilizing' and 'functional cure' terminologies were used recently to denote the case of an "exceptional EC", Loreen Willenberg (second author)–also referred to as 'The San Francisco patient'.[77] After sampling over 184 million $CD4^+$ T cell genomes from Loreen's body, Yu and colleagues could not detect any replication-competent or intact DNA.[77,78] What is most impressive is that this exceptional control phenomenon occurred without the use of ART or any other intervention. Loreen's unique case challenges the boundaries of available terminology in the HIV cure-related field. In light of Loreen's case, Zerbato and Lewin proposed that a 'cure' for HIV could also be defined as having no replication-competent HIV, rather than the absence of detectable virus.[45] In 2014, Colson and colleagues described two similar 'endogenization' cases, where patients presented with integrated viral HIV DNA in their genomes but had no viable HIV production.[79] Researchers postulated that this 'functional cure' occurred through a gradual process of HIV deactivation caused by an unusually high presence of stop codons in the patients' genome.[79] Authors also proposed a new vision for HIV 'cure' through "integration, inactivation and potential endogenization of a viral genome into the human genome."[79] Similarly, Casado and colleagues analyzed three cases of "exceptional ECs" who never expressed signals of clinical disease progression while off ART for over 25 years.[31] These individuals exhibited a combination of beneficial factors, such as host protective alleles, low levels of total HIV DNA, low frequencies of intact genomes, strong cellular HIV-specific immunity, and a high poly-functionality index.[31] They were thought to have experienced a "spontaneous functional HIV-1 cure" due to HIV replication impairment; however, they were highly heterogenous with respect to their clinical, virologic, and immunological characteristics.[31] Additional work will be needed to define individuals such as these and to determine how they might inform the field.

Finally, another question that remains unsettled is the degree to which a 'functional cure' regimen must control viremia. For example, it would be a huge scientific achievement if individuals on ART could undergo therapy and maintain a lower viral set point. However, would this set point meet the currently-accepted U = U standards, which would require viral load to remain below 200 copies/mL for HIV to be untransmissible? Would it result in inflammatory consequences that would make withholding ART untenable? The degree of viremia following control interventions needs to be further explored in the U = U era and represents an area where greater consensus is needed. This question also brings into focus potential tensions between acceptable definitions for the scientific community and for PLWHIV and their advocates.

Preliminary considerations

In light of the above discussion, we, as a multi-disciplinary group of socio-behavioral scientists, PLWHIV, community advocates, medical students, and biomedical researchers who have collaborated in various ways on HIV cure research for over a decade, make the following three proposals:

1) The scientific community should cease using the expression 'functional cure'. As denoted above, there is no shared consensus about what the term means. 'Functional cure' has been used to describe a range of conditions, and it is confusing to multiple audiences, including those living with HIV.
2) Studies should be described in relation to the outcomes they are attempting to achieve. This is especially true for recruitment materials, study names and informed consent documents.[80,81] We suggest using descriptive terms like 'ART-free durable viral suppression', 'durable ART-free control', or 'absence of replication- or rebound-competent HIV' when describing health states that are the goals or results of studies. The word 'cure' may hold more salience for and be better applied to advocacy and funding contexts.[46] Further, expressions like 'rebound-(in)competent' should have lay explanations to accompany them.
3) Where feasible, members of communities who are the focus of the research should be involved in determining language used for study recruitment and informed consent documents. This may be done via Community Advisory Boards (CABs) and other community engagement efforts. We suggest avoiding using conceptual terms such as 'functional cure' and 'remission' altogether. The field should also engage clinicians, communities, regulators, ethicists, and researchers in defining proper terminology to denote meaningful ways to describe ART-free viral control that either falls short of complete elimination or whose apparent durable elimination remains unknown. Greater attention should be paid to understanding and respecting diverse linguistic, cultural, and community contexts in shaping the meanings and understandings associated with terminology, biomedical therapeutics, and practices.

Table 1 summarizes possible alternatives for 'functional cure', depending on which theme is emphasized – although this list is not exhaustive.

Table 1
Possible alternatives to 'functional cure'.

Themes Emphasized	Alternatives to 'Functional Cure'
With Intervention	
Suppression	*HIV suppression in the absence of ART*
	Suppression of HIV without ARV
	Viral suppression off treatment
	Drug-free durable suppression
	Durable viral load suppression (off treatment or ART)
	Durable suppression (off HIV treatment or ART)
	Durable ART-free viral suppression
	Virologic suppression off therapy (VSOT)
Control	*Post-treatment control*
	Post-treatment viral control
	Durable control (off HIV treatment or ART)
	Drug-free long-term control
	Drug-free viral control
	Sustained viral control (off HIV treatment or ART)
	Immune control
	Immune-mediated control (of virus)
	Post-intervention control
	Durable ART-free suppression
	Durable virologic control
Other	*Undetectable off HIV treatment (or ART)*
	Sustained virologic response
Without Intervention	
	Natural immunity
	Natural suppression
	Spontaneous control
	Elite control
	Exceptional control

Conclusions

In sum, this paper revisited the 'functional cure' nomenclature. We described how this apparent internally contradictory term can be confusing, conflated, and simplistic. The flawed and reductionist dichotomy of 'sterilizing' *versus* 'functional' cure terminology is not helpful, because it fails to account for various occurrences of 'cure,' patient and community perspectives, and scientific realities. We call for greater consideration of the language used to describe HIV cure-related research and its possible outcomes, and for continued, significant, and strategic engagement to ensure acceptable and accurate terminology. As the landscape of HIV therapeutics continues to evolve and as scientific discoveries flourish, so should our discourses and the words we use to describe them.

Declarations

Ethics Approval and Consent to Participate.

Not applicable. This manuscript did not involve human participants, human data or human tissue.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data not contained in the peer-reviewed literature.

Availability of data and material

Not applicable.

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Author's contributions

KD draft the initial version of this manuscript.

LW, LD, LS, JT, CR, DP, DC, LN, HP, KEP, JK, JG, BB, PS, JAS, MJP reviewed the manuscript for intellectual contents.

All authors thoroughly read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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