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What we talk about when we talk about durable viral suppression

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Summary

As policies built on “Undetectable = Untransmittable” become more popular, use of durable viral suppression (DVS) as an outcome in analyses is increasing. We identified a case series of recent HIV-related publications that study the DVS outcome. The majority did not distinguish between a definition of DVS and the operationalization of that definition. Clearer discussion of DVS, including a formal definition, is needed to ensure better comparability across studies and ultimately better public health outcomes.

Keywords

HIV infection; persons living with HIV; viral suppression; durable viral suppression; sustained viral suppression

Among persons living with HIV (PLWH), one goal of HIV care and treatment is achieving an undetectable viral load. Viral suppression confers benefits at both the individual and public health-level[1-4]. Strong evidence supports that PLWH cannot sexually transmit HIV to others when their viral load is ≤ 200 HIV RNA copies/mL and they have been adherent to antiretroviral therapy for at least 6 months – a finding summarized by the now widely used expression “Undetectable = Untransmittable” or “U=U”[5,6].

In the context of data demonstrating the importance of achieving and maintaining a suppressed viral load[5,7], there has been increasing interest in measuring so-called durable (or sustained) viral suppression (DVS) in clinical and epidemiologic studies[8,9]. A person might be classified as having DVS if all viral loads taken during a period (typically 2-4 viral loads per calendar year, though many individuals have only one per calendar year[10,11])

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were suppressed. However, initial reading of the literature suggests that scientists have not settled on a formal definition of DVS, which is essential for comparison across studies.

To explore this issue, we conducted a PubMed search of HIV-related publications from highly-cited journals that publish HIV-related research and identified 10 recent papers (as of 05/15/2019) that used durable viral suppression as an outcome and met additional search criteria (see Appendix for details). Our goal was to use this case series – a small convenience sample of 10 published papers – to illustrate the infrequency of clearly-stated DVS definitions by examining whether investigators provided two characteristics: 1) the *definition* of DVS that they want to measure and 2) the *operationalization of that definition* used for classifying individuals as having DVS or not.

All 10 papers provided an operationalized definition. The majority (8/10) classified the outcome as all viral loads suppressed during a period (based on calendar time or anchored by timing of an individual's viral load results; Table 1[9,12-20]). The remaining two classified the outcome as “repeated HIV RNA measurements below the limit of quantification”[15] and “HIV viral loads <200 copies/mL at the last two test results in the 12-month measurement period”[16].

Only 2/10 papers suggested an underlying *definition* for DVS that they aimed to measure, thus distinguishing between the definition and the way in which that definition was operationalized for analysis[17,20]. Of these two papers, Enns et al. provides the more explicit distinction stating (emphasis added) “Sustained viral suppression was *defined* as being virally suppressed at last viral load and having evidence of *consistent viral suppression for at least 12 months prior*... Thus, to be *classified* as having achieved sustained viral suppression, patients must have had a viral load of < 200 copies/mL at least 12 months prior to their last...test, as well as suppressed status on any intervening ...test results.” The other definition by Nwangwu-ike et al. was similar (“consistent viral suppression during the past 12 months”).

Strictly read, the classification (i.e., the operationalized definition) given by Enns et al. would hold if there were zero, or eight, or 18 intervening viral load tests. Under such a classification, if the probability of correctly classifying a person with viral suppression as virally suppressed is p (a constant attribute of the assay), a person who truly had DVS and received N tests over a given period would have a risk of being found to be “not having DVS” of $(1-p)^N$, assuming independent errors. In such a situation, *the risk of falsely classifying an individual with DVS as not having DVS will increase with the number of viral load tests that person receives*. Only one paper in our search discussed that the probability of misclassifying DVS could vary by test frequency[9]. In other words, differential misclassification of DVS by number of tests needs to be considered whenever DVS is used or interpreted.

In summary, we found that most studies (8/10) did not articulate an underlying definition of DVS, and therefore did not make a distinction between the definition of DVS and the way in which DVS was classified in analysis. The two studies that did make a distinction both

defined the underlying definition of DVS as *consistent* viral suppression, without specifying how many tests, or at what interval, constituted consistency.

Clarification and consensus concerning the underlying definition of DVS is needed for several reasons. First, the adequacy of operationalized DVS classifications can only be evaluated if there exists a clearly-defined, underlying construct of interest. Then, DVS classifications can be evaluated in terms of their departure from the “true” construct and details of the potential classifications can be thoughtfully debated. One challenge will be how to account for viral “blips”, which if >200 HIV RNA copies/mL and captured by a viral load test would exclude an individual from being categorized as having DVS under most classification strategies. While “blips” have little clinical significance, co-occurrence of a blip and an event that has potential for HIV transmission could be problematic[21,22]. Of note, the preferred operationalization of the DVS definition might depend on the intended use of DVS in a particular setting (e.g., clinical compared with research use). Specifically, preference for whether a classification strategy maximizes sensitivity or specificity may be context-dependent. Second, evidence suggests that maintaining suppression (measured by the current recommended viral load testing frequency) is sufficient for preventing HIV transmission between serodiscordant couples[7]. However, the measurement gold standard implied by the underlying definition (e.g., measuring daily viral suppression is arguably the gold standard corresponding to the hypothetical underlying definition “every day suppressed”) is essential information for evaluating misclassification of operationalized DVS estimates, even if said gold standard were infeasible to implement in practice. Finally, a clear definition will allow for explicit discussion of the assumptions implied by various DVS classifications and enable future work examining whether misclassified DVS estimates vary by patient or provider characteristics.

The benefits promised by U=U have been met with great enthusiasm and an increase in the use (and call for use) of so-called durable viral suppression measures for examining health outcomes. We hope this brief communication spurs more thorough discussion of the definition of DVS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Durable viral suppression classifications and presence of a distinction between underlying definition and operationalized definition of durable viral suppression in ten recent HIV-related articles.

Table 1.

Article	Relevant outcome of interest	Outcome classification in analysis	Durable viral suppression classification type	Viral load frequency used as a criterion for either DVS/SVS outcome determination or analytic sample inclusion?	Distinction between the definition and the operationalized version of definition used for classification?	Details of distinction if applicable
Jefferson et al. Place-based predictors of HIV viral suppression and durable suppression among heterosexuals in New York City	Durable viral suppression	Achieving the following within 12 months of HIV diagnosis: "(A) had at least two suppressed (< 200 cc/mL) viral load tests that were at least 90 days apart from one another with no intervening unsuppressed (>200 cc/mL) viral load tests, and (B) had no unsuppressed viral load tests after they had achieved durable viral suppression"	All results suppressed during time period	Yes; "at least two suppressed" required to be considered durable	No	
Nyaku et al. Non-persistence to antiretroviral therapy among adults receiving HIV medical care in the United States	Sustained viral suppression	"all viral loads documented in the patient's medical record as undetectable or <200 copies/mL during the past 12 months"	All results suppressed during time period	Yes; at least one viral load result required to be considered sustained	No	
Chowdhury et al. Clinical outcomes of young Black men receiving HIV medical care in the United States, 2009–2014	Durable viral suppression	"all viral load measurements documented undetectable (<200 copies/mL) in the past 12 months"	All results suppressed during time period	Yes; at least one viral load result required to be considered durable	No	
Gulhati et al. Higher levels of angiotensin-II are associated with early and sustained viral suppression in children living with vertically acquired HIV	Proportion of life with sustained viral suppression (note: sample only includes children)	"the sum of all periods during which SVS was achieved in days (numerator) divided by patient age in days (denominator)"	function of sustained viral suppression defined as "repeated" measurements suppressed	Yes; sustained viral suppression ("repeated HIV RNA measurements below the limit of quantification by the clinical virology laboratory at each center (target not detected, 20, or 40 copies/mL)") required for study inclusion	No	
Byrd et al. Adherence and viral suppression among participants of the Patient-centered HIV Care Model project—a collaboration between community-based pharmacists and HIV clinical providers	Sustained viral suppression	"defined as HIV viral loads <200 copies/mL at the last two test results in the 12-month measurement period"	Last two measurements suppressed	Yes; "the sustained viral suppression analysis required 2 viral load results" in each measurement period for inclusion in analysis	No	Methods section, Patient Outcomes; distinction between
Enns et al. HIV Care trajectories as a novel longitudinal assessment of retention in care	Sustained viral suppression	"must have had a viral load of < 200 copies/mL at least 12 months prior to their last viral load test, as well as suppressed status on any intervening viral load test results"	All results suppressed during time period	Yes; results from at least two viral load tests required to be considered sustained	Yes	

Article	Relevant outcome of interest	Outcome classification in analysis	Durable viral suppression classification type	Viral load frequency used as a criterion for either DVS/SVS outcome determination or analytic sample inclusion?	Distinction between the definition and the operationalized definition used for classification?	Details of distinction if applicable "defined" and "classified" SVS
Beattie et al. Multilevel Factors Associated with a Lack of Viral Suppression Among Persons Living with HIV in a Federally Funded Housing Program	Lack of durable viral suppression	"any HIV viral load test reported to the Registry during the observation period (12 months) being greater than 200 copies/mL"	All results suppressed during time period	Yes; at least two viral load results within the 12-month observation period required for sample inclusion	No	
Lemons et al. Opioid Misuse Among HIV-Positive Adults in Medical Care: Results From the Medical Monitoring Project, 2009–2014	Durable viral suppression	"all HIV viral load measurements documenting undetectable or <200 copies/mL during the 12 months preceding the interview"	All results suppressed during time period	No; however, data source used is a sample of persons in care	No	
Robertson et al. Impact of an HIV Care Coordination Program on Durable Viral Suppression	Durable viral suppression	"defined DVS as regular VL monitoring and all VLs < 200 copies per milliliter in months 13–36 of follow-up"	All results suppressed during time period	Yes; at least 2 viral load results in the 2-year period to be included in analysis and regular viral load monitoring ("...having 1 VL in each 12-month period of follow-up and 90 days between the first and the last VL reported during months 13–36") required to be considered durable	No	Methods section of abstract; a definition of SVS provided in parentheses, "sustained viral suppression (consistent viral suppression during the past 12 months)"
Nwangwu-Ike et al. Racial and Ethnic Differences in Viral Suppression Among HIV-Positive Women in Care	Sustained viral suppression	"Sustained viral suppression is based on 1 viral load tests (ie, all viral load values, undetectable or <200 copies/mL) in medical records during the 12 months before the interview date"	All results suppressed during time period	Yes; at least one viral load result required to be considered sustained ("Sustained viral suppression is based on 1 viral load tests")	Yes	

Abbreviations: DVS = durable viral suppression; SVS = sustained viral suppression