CLINICAL GUIDELINES PROGRAM
NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV • HCV • STIs • SUBSTANCE USE • LGBTQ+ HEALTH

U=U Guidance for Implementation in Clinical Settings

Updates, Authorship, and Related Resources

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What Is U=U?

People who achieve and maintain an undetectable HIV viral load do not sexually transmit HIV.

This scientific finding, called "Undetectable = Untransmittable," or "U=U," has been promoted as a health equity initiative by the Prevention Access Campaign since 2016 and has been endorsed by the U.S. Centers for Disease Control and Prevention, the New York City Health Department, the New York State Department of Health (NYSDOH), and many other health departments and experts. U=U asserts that individuals who keep their viral load below the level of assay detection (typically HIV RNA <20 copies/mL) do not pass HIV through sex. Leading scientists have assessed the evidence base as "scientifically sound" [Eisinger, et al. 2019].

As emphasized in the NYSDOH U=U Policy Statement, the U=U concept is a "driving force to accelerate the achievement of New York State's Ending the Epidemic goals." Specifically, U=U aligns with numerous efforts to dismantle HIV-related stigma and improve the health, well-being, and self-esteem of all people living with HIV, particularly by removing fear from their sexual and romantic relationships and combating the isolation they may experience. The statement further elaborates: "Endorsing U=U opens a new and hopeful chapter in New York State's HIV epidemic, creating unprecedented opportunities for New Yorkers living with HIV and the institutions that serve them."

Evidence Base Supporting U=U

Evidence from the last 3 decades has established that adherence to HIV antiretroviral therapy (ART) suppresses viral replication, improves the health of people with HIV, and reduces the risk of sexual transmission. These data have accumulated from a randomized clinical trial, observational cohort studies, and ecological studies correlating incidence and viral suppression rates in communities.

There is an overwhelming body of evidence indicating that people who achieve and maintain viral suppression (HIV RNA <200 copies/mL) do not transmit HIV through sex [Eisinger, et al. 2019]. The HPTN 052 randomized clinical trial and 3 observational cohort studies, PARTNER, PARTNER 2, and Opposites Attract, evaluated the effect of viral suppression in preventing HIV transmission [Rodger, et al. 2019; Bavinton, et al. 2018; Cohen, et al. 2016; Rodger, et al. 2016]. The studies followed thousands of male and heterosexual couples in which one partner had HIV and the other did not (i.e., serodifferent couples) and documented no genetically linked HIV transmissions when the partner with HIV was taking ART and was virally

suppressed. In the PARTNER2 and Opposites Attract studies, anal sex without condoms was reported more than 88,000 times among serodifferent couples of men who have sex with men, and vaginal or anal sex without condoms was reported 36,000 times among heterosexual serodifferent couples—all without any linked transmissions.

These studies provide robust evidence that individuals *do not* sexually transmit HIV if they are virally suppressed (HIV RNA <200 copies/mL) or have an undetectable viral load (typically HIV RNA <20 copies/mL).

Glossary

- **Viral load suppression:** A measured quantitative HIV RNA level <200 copies/mL in blood
- **Undetectable viral load:** An HIV viral load that is below the level of detection on a specific assay, typically HIV RNA <20 copies/mL to 50 copies/mL
- **Durably undetectable:** An undetectable viral load maintained for at least 6 months. This indicates that an individual's undetectable HIV viral load is stable and *they will not transmit HIV* through sex if they continue to adhere to treatment.
- **Untransmittable:** As established by various clinical trials and observational studies, individuals who maintain an undetectable viral load have so little HIV in their blood and other secretions that they have no risk of passing HIV to others through sex.
- **Virologic blip:** When an individual's HIV is initially undetectable on a viral load test, then is at a low but detectable level on a repeat viral load test (usually HIV RNA of 20 to 200 copies/mL, but can be higher), and is again measured at an undetectable level shortly thereafter.

Application to Clinical Practice

The concept of U=U is grounded in the following principles [Eisinger, et al. 2019]:

Adherence: For HIV treatment to provide maximum benefit, it is essential that ART is taken as prescribed; the goal is to achieve an undetectable viral load. Achieving an undetectable viral load can require ART for up to 6 months. Once an undetectable viral load is achieved, continued adherence to ART is required to ensure that the virus remains suppressed so it is not transmitted through sex.

Because *maintaining* an undetectable viral load is foundational to the U=U strategy and may be functionally challenging for many individuals with HIV, it is recommended that consistent adherence to ART is demonstrated before relying on U=U as a sole, effective HIV prevention strategy. Consistent adherence may be confirmed with:

- Two consecutive undetectable viral load test results separated in time (e.g., by at least several weeks or more); *or*
- A full 6-month period during which all viral load test results are undetectable (more conservative)

If an individual stops or is inconsistent in taking ART, they may no longer have an undetectable viral load or may be at high risk of recrudescent viremia. In this scenario, transmission is possible; viral load must be undetectable for U=U to be an effective HIV prevention strategy.

Monitoring: Per NYSDOH AI guidelines, viral load testing should be performed every 4 months after an individual achieves an undetectable viral load. If viral suppression and stable immunologic status are maintained for >1 year, then viral load testing can be extended to every 6 months in select patients thereafter.

Best Practices

Adherence: U=U assumes that an individual is adherent to HIV treatment and is consistently taking antiretroviral medications as prescribed, which is the only way to maintain an undetectable viral load. Suspension of ART adherence or intermittent adherence may lead to a viral rebound, negating the effectiveness of U=U as a stand-alone HIV prevention strategy. Care providers should ask patients if anything might make it difficult for them to consistently take their medicines and address any likely barriers to adherence, which may include poverty, housing instability, and other key social factors, and offer all available support, referrals for assistance, and other interventions, along with HIV prevention strategies that do not rely on viral suppression (see NYSDOH Retention and Adherence Programs in Medical Settings).

Viral load monitoring: Care providers should follow existing NYSDOH AI guidelines for monitoring viral load in patients on treatment.

Screening and treatment for sexually transmitted infections (STIs) other than HIV: The use of effective alternatives to condoms to prevent HIV—including pre-exposure prophylaxis (PrEP) and HIV treatment—may reduce condom use and may require more careful monitoring of other STIs, including at extragenital sites.

- Care providers should already be encouraging all patients to get tested for STIs; using U=U as a strategy to prevent HIV transmission provides an additional opportunity to remind patients of the importance of regular screening for other STIs.
- Care providers should consider offering STI screening every 3 months for all individuals with HIV who rely on U=U as a sole strategy to prevent the sexual transmission of HIV; this is the same screening frequency recommended for those taking PrEP.

Special Topics

Virologic blips and U=U: Patients on previously suppressive ART may occasionally experience low-level transient viremia (a "blip"; see definition in Glossary). Isolated blips are not considered a sign of virologic failure.

Virologic blips likely occurred in individuals participating in the HPTN 052, PARTNER, PARTNER 2, and Opposites Attract studies, yet there was no transmission from people whose measured HIV viral load was consistently suppressed. This demonstrates that people with HIV whose tested viral load levels remain undetectable or suppressed do not sexually transmit HIV, even if they have temporarily detectable but low levels of HIV during virologic blips while adherent to their medications.

HIV RNA in genital secretions and U=U: In research studies, 8% to 16% of semen samples from men with HIV had detectable virus despite undetectable HIV RNA in blood plasma [Kantor, et al. 2014; Sheth, et al. 2009]. A similar dynamic holds for residual virus in vaginal secretions [Olesen, et al. 2016]. There is no evidence that detectable virus in genital secretions while plasma viral load is undetectable is associated with transmission. Detectable virus in genital secretions likely occurred in HPTN 052, PARTNER, PARTNER 2, and Opposites Attract; however, there was no transmission from people whose measured HIV load was consistently suppressed.

U=U and HIV transmission through breastfeeding: See the NYSDOH AI guidance NYS Good Practices to Prevent Perinatal HIV Transmission > Infant Feeding.

U=U and HIV transmission through sharing of injection drug equipment: Studies demonstrate that ART *greatly reduces* the risk of HIV transmission through sharing of injection drug use equipment [Wood, et al. 2009]. However, research *has not* established that people with an undetectable HIV viral load do not transmit HIV through needle sharing.

U=U and needlestick injuries: Research *has not* established that people with an undetectable HIV viral load do not transmit HIV to people who are stuck by a needle containing their blood. HIV post-exposure prophylaxis (PEP) may be indicated.

Ensuring equitable access to knowledge about U=U: Research has established that certain groups, including sexual and racial or ethnic minority groups, report decreased awareness of or are less likely to be counseled on U=U [Card, et al. 2022; Grace, et al. 2022; Carneiro, et al. 2021; Rivera, et al. 2021]. Care providers are encouraged to make an extra effort to ensure that all patients with HIV are made aware of the importance of U=U and its implications.

Counseling Individuals About U=U

Care providers should inform all patients of the following: "People who keep their HIV viral load at an undetectable level by consistently taking HIV medications will not pass HIV to others through sex."

Sharing this message with *all* patients can help accomplish the following:

- Diminish stigma associated with having HIV
- Reduce barriers to HIV testing and treatment
- Increase HIV testing uptake
- Inform choices about whether or not to start or continue an HIV prevention method
- Increase interest in starting and staying on antiretroviral therapy (ART)

- Improve self-esteem by removing the fear of being contagious
- Support healthy sexuality regardless of HIV status
- Reduce sex partners' concerns

Providing this message is important regardless of the patient's current sexual activity, as many people living with HIV maintain celibacy because of the fear and anticipatory guilt of potentially transmitting HIV. This message is also important for all individuals, not only those living with HIV, to reduce overall stigma and increase uptake of HIV prevention methods and HIV testing.

Encourage patients newly diagnosed with HIV and those previously diagnosed but not taking ART to immediately start (or restart) treatment.

Explain that doing so will help them avoid damage to their body and immune system and will prevent transmission of HIV to their sex partners.

- The importance of ART should be framed primarily in terms of helping the individual with HIV maintain personal health. Prevention of transmission is a secondary, fortuitous effect of HIV self-care.
- Initiation of ART as soon as possible after diagnosis, even on the same day as diagnosis or at the first clinic visit, improves long-term outcomes, such as virologic suppression and engagement in care at 12 months [Ford, et al. 2018]. Extensive support is available to people living with HIV for adherence to treatment and engagement in care.

Provide the following information about U=U to patients (proposed language in italics):

- *Keeping your HIV undetectable helps you live a long and healthy life.*
- *To get your HIV to an undetectable level and to keep it undetectable, take antiretroviral medicines as prescribed.*
- *It may take up to 6 months of taking HIV treatment medicines to bring your HIV down to an undetectable level.*
- *If your HIV is undetectable and you are taking your medications as prescribed, you can be sure you will not pass HIV through sex.*
- *People who keep their HIV at an undetectable level will not pass HIV to others through sex.*
- *If you stop taking HIV medicines, your HIV can rebound to a detectable level within 1 to 2 weeks, and you may pass HIV to your sex partners.*
- *Keeping your HIV at an undetectable level helps you safely conceive a child with your partner.*

Counsel patients to share information about the research on U=U as follows (proposed language in italics):

In 4 research studies that involved thousands of couples, no one who was on HIV treatment and whose HIV was undetectable passed HIV to their HIV-negative sex partner.

Counsel patients with virologic blips that U=U still applies to them:

Reassure patients who may be worried or concerned about virologic blips. Explain that people who have virologic blips do not transmit HIV sexually as long as they continue to take ART consistently.

Advise patients that they can share the following personal information with current or potential sex partners:

- When they last had a viral load test and if their viral load was undetectable
- **Note:** Individuals should tell partners that their HIV is undetectable only if they have taken HIV medicines consistently since their last test with an undetectable viral load.

Care providers should encourage all sexually active patients and their partners, particularly those who do not use condoms consistently, to get tested regularly for bacterial sexually transmitted infections (STIs).

- Regular testing and prompt treatment can reduce transmission of bacterial STIs among individuals and throughout the population.
- It is also important to inform patients that common STIs may be asymptomatic.

Counseling Couples About U=U

Care providers should counsel *all* patients on strategies to maintain a healthy, fulfilling, and worry-free sex life, including the use of HIV treatment, condoms, pre-exposure prophylaxis (PrEP), and emergency post-exposure prophylaxis (PEP).

Counseling for couples in which one partner has HIV can include the following:

- **HIV treatment:** Couples may decide that antiretroviral therapy (ART) and an undetectable viral load for the partner with HIV provides sufficient protection against HIV transmission.
- **PrEP:** PrEP is a safe and effective daily pill or long-acting injection that prevents HIV infection. The partner without HIV may decide to take PrEP if they:
  - Are unsure that their partner's HIV viral load is undetectable, especially if their partner has only recently started ART
  - Have more than 1 sex partner
  - Feel more secure with the added perception of protection provided by PrEP
- **PEP:** After a possible HIV exposure (e.g., if a sex partner with HIV has not consistently taken ART or is not virally suppressed), the immediate initiation of emergency PEP can prevent HIV infection.
- **Condom use:** Condoms protect against other STIs, such as gonorrhea, chlamydia, and syphilis, and help prevent pregnancy.

Counsel patients to find a prevention strategy that works for them.

- If an individual who does not have HIV is unsure if their partner has an undetectable level of virus or is anxious about acquiring HIV, care providers should encourage that individual to choose a prevention strategy that works for them, whether that is use of PrEP, emergency PEP, condoms, or a combination of these strategies.
- Care providers should emphasize that no one should ever be compelled to have sex without condoms.

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Supplement: Guideline Development and Recommendation Ratings

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding source	NYSDOH AI
Program manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff.
Mission	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
Expert committees	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations.
Committee structure	• Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor • Contributing members • Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Disclosure and management of conflicts of interest	• Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation. • The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member.
Evidence collection and review	• Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. • A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.
Recommendation development	• The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee's expert opinion. • The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Review and approval process	• Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. • Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External reviews	• External review of each guideline is invited at the developer's discretion. • External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.
Update process	• JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations. • If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates and will invite full committee review as indicated.

Table S2: Recommendation Ratings and Definitions		
Strength	**Quality of Evidence**	
A: Strong B: Moderate C: Optional	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
	*	Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial.
	2	Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes.
	2†	Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline.
	3	Based on committee expert opinion, with rationale provided in the guideline text.