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Perceptions of U = U Among Italian Infectious Diseases Specialists: A Nationwide Survey on Providers' Attitudes Toward the Risk of HIV Transmission in Virologically Suppressed Patients

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Abstract

This survey aimed to understand how far the Italian infectious diseases (ID) specialists are confident in the ''Undetectable = Untransmittable'' (U = U) message and translate this concept into clinical practice. An anonymous survey was distributed by e-mail to 286 clinicians to collect their opinions regarding six situations potentially at risk of HIV transmission between virologically suppressed patients and seronegative individuals who possibly require postexposure prophylaxis (PEP). Overall, 51% of ID specialists deemed zero risk of HIV transmission through condomless sex for undetectable patients. This answer was more frequent among HIV specialists (30% vs. 21%, $p = .01$) and clinicians working in teaching hospitals (35% vs. 16%, $p = .03$). Remarkably, 61% of participants would advise taking PEP for the HIV-negative partner in case of sexual intercourse with a seropositive person with a recent blip occurrence or absence of an HIV RNA test performed within the last 6 months (63%). Seventy-three percent of respondents deemed it essential to know patients' history of adherence to interpreting an HIV RNA test, regardless of its timing. When applying the U = U concept to daily clinical decisions, we observed an overall cautious attitude among physicians. Concerns mainly regarded the timing of the last HIV RNA test to the exposure event, especially in the absence of details on the patient's adherence. Wider diffusion and application of the U = U message are needed.

Keywords: U = U, HIV, survey, HIV providers, PEP

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Introduction

PROSPECTIVE, OBSERVATIONAL, MULTICENTRIC studies performed in Europe have documented no cases of within-couple HIV transmission among many heterosexual and male homosexual serodiscordant couples reporting condomless sex with the HIV-positive partner using suppressive Antiretroviral Therapy.[1,2]

This evidence suggests that the risk of HIV transmission through condomless sex in serodiscordant couples of people living with HIV (PLWH) is effectively zero with suppressed HIV viral load.

This remark is one of the most significant advancements in HIV over the last 25 years and represents the basis of the concept of Treatment as Prevention.[3]

In 2016, these findings supported the message of ''Undetectable = Untransmittable'' (U = U), launched during the Prevention Access Campaign to scale up the previously mentioned findings from the scientific world to the broad public and with the ultimate goal of reducing the stigma surrounding chronic HIV infection.[4]

Increasing the awareness in the community about the fact that the achievement of stable undetectable viral load prevents sexual HIV transmission by seropositive individuals would increase the motivation for HIV testing among people uncertain of their serostatus and reduce the anxiety about HIV acquisition among seronegative subjects, ultimately leading to public health benefits in terms of decreased HIV transmission.[5]

In light of these considerations, knowledge and comprehension of U = U messages among patients diagnosed with HIV should be increased by infectious diseases (ID) specialists as means to promote their motivation to adhere to antiretroviral regimens to reach and maintain undetectable viral load.[6]

Surprisingly, physicians' opinions collected so far about this topic outline that HIV care providers are reluctant to systematically discuss the U = U concept and its implication with patients, primarily because of personal disbeliefs or paternalistic/moralistic views.[7]

In Italy, the care for PLWH has historically been provided almost entirely in HIV specialist clinics. Currently, the management of chronic HIV infection is mainly hospital centered, with a predominant role of ID specialists and limited involvement of other health care figures.

The present is the first survey intended to explore the perceptions of Italian ID specialists about the risk of HIV transmission in virologically suppressed patients and to understand the recommendations that they are currently providing in clinical practice for postexposure prophylaxis (PEP).

Investigating providers' opinions and attitudes toward U = U message diffusion and PEP prescription in this country could lead to discovering unexpected perspectives, also considering the Italian historical and cultural background role that could influence clinicians' choices.

Methods

The ''Real Time Study Group'' (see the Acknowledgments section) is a collaborative cohort including 15 Italian ID centers that share anonymous clinical and sociodemographic information of PLWH, intending to perform research projects that could ultimately increase their quality of care.

Currently, HIV care in Italy is in charge of 5,471 hospital-centered ID specialists covering 141 ID units and is entirely reimbursed by the National Health Care System.[8] Following the last HIV-care national guidelines,[9] PLWH under combined Antiretroviral Therapy with stable undetectable viral load and satisfying immunological condition receive one specialist visit and one blood test every 3 months in media.

We distributed an anonymous online survey to all clinicians working in the ''Real-Time Study Group'' from November 1 to December 30, 2019.

Both teaching (university) and nonteaching hospitals were involved.

In the first part of the questionnaire, we asked clinicians to provide sociodemographic information (sex, age, years of professional activity as ID specialists). They should specify the affiliation to a teaching or nonteaching hospital and add a few data regarding the geographical position and the number of HIV patients in charge of the center. Providers should also specify if HIV represented their prevalent activity (HIV specialists) and, in this case, the number of years spent working in this position.

The questionnaire content was adjusted to fit the Italian health care and cultural scenario. Questions described six different clinical situations requiring the evaluation of the risk of HIV sexual transmission between virally suppressed HIV-infected patients and their partners through condomless sex (Scenario 1), procreative sex (Scenario 2), in case of recent viral blip occurrence (Scenario 4), or absence of a recent HIV RNA test (Scenario 6). We also considered the event of occupational exposure to an HIV-positive patient with an undetectable viral load (Scenario 3). Finally, experts' opinions about the reliability in time of an HIV RNA test in the clinical decision-making process were retrieved (Scenario 5).

Each clinical scenario was clearly defined, leading to a direct question followed by three to seven multiple choice answers, aimed to investigate clinician's recommendations (including PEP prescription) according to their perception of the actual risk of HIV transmission in the setting of virological suppression. One single answer was considered valid.

Our working group self-designed the survey tool, and all coauthors independently assessed its content validity. A pilot version of the questionnaire was preliminarily performed on a small subset of participants (10 subjects for each center) by two independent researchers in the Infectious Diseases Unit of Foggia University Hospital and Bergamo Giovanni XXIII Hospital, respectively. Researchers personally performed accompanied interviews to assess the face validity of the survey and to outline and eliminate possible confounding elements.

The final version of the survey was anonymous and written in the Italian language. Participation in the survey was wholly voluntary, and respondents were not remunerated.

A contact person was identified among the medical staff members in each of the 15 participating centers, who was responsible for receiving the questionnaires by e-mail by the coordinating center (Unit of Infectious Diseases, Papa Giovanni XXIII Hospital, Bergamo), distributing the survey to the rest of the medical personnel, and integrating the answers in a shared case report form (CRF).

Once completed, we forwarded the CRFs to the coordinating center and performed the statistical analysis.

Descriptive statistics of the sociodemographic variables were performed in terms of medians (1st quartile–3rd quartile, q1–q3) for continuous nonparametric distributed variables and in terms of absolute frequencies (percentage) for categorical variables.

As appropriate, the Pearson χ^2 test/Fisher exact test was used to compare the answers given in the six already mentioned scenarios by clinicians working in teaching versus nonteaching hospitals. The same analysis was performed on answers collected among respondents who stated to be HIV specialists versus practitioners not involved in the HIV field.

The analysis aimed to outline if belonging to larger teaching centers or having a long experience in the field of HIV could reflect on the level of confidence in the U = U message and affect clinicians' attitudes toward PEP prescription in borderline clinical situations.

Analysis was performed using Jamovi 1.8.4. A $p < .05$ was considered statistically significant.

Ethical approval

Participation in this survey was wholly voluntary and addressed to ID specialists.

No patients were enrolled in this study, and the survey did not imply sensitive information or patients' data. The collected answers were anonymous, so it was impossible to identify the respondent physician. Moreover, participants were not remunerated.

The Ethics Committee of the Coordinating Center (Bergamo Papa Giovanni XXIII Hospital) was consulted for ethical approval and deemed ethical approval unnecessary in light of the specific study design.

Consent to participate

No formal consent to participate was requested, as completing the questionnaire implied consent. We requested written informed consent for all the physicians enrolled in the study for the publication of the collected data.

Results

Two hundred eighty-six clinicians, 45% males, filled in the survey.

Of them, 179 (63%) worked in teaching hospitals, and 136 (47%) stated that HIV represented their prevalent field of interest as ID specialists.

The main sociodemographic features of respondents are reported in Table 1. Notably, comparing HIV and non-HIV-specialists among respondents, no significant differences were found regarding sex, age, and years of working as ID specialists. Proportional distribution of participants in centers from northern, middle, and southern Italy was reported.

Survey items and frequency of answers collected overall and based on the working situation (working in teaching vs. nonteaching hospitals and HIV vs. non-HIV specialists) are reported in Tables 2 and 3.

In the first scenario (condomless sex), 144 interviewed physicians (50%) affirmed that the risk of HIV transmission through condomless sex for virologically suppressed patients is zero (answer 1), while 60 subjects (21%) affirmed recognizing an ''extremely low'' level of risk (answer 2). Summing up answers 1 and 2, the total percentage of clinicians who reported being confident in the absence of sexual transmission was $\sim$70%.

Notably, 50% of clinicians working in university centers (139 subjects) showed confidence in the U = U message, choosing options 1 or 2, versus 21% (65 clinicians) of providers working in nonuniversity centers ($p = .03$). We noticed a similar disparity among the answers provided by clinicians involved in HIV care as their prevalent or nonprevalent medical activity: 39% of HIV specialists (109 clinicians) affirmed to believe in zero or extremely low risk of transmission in the condition mentioned above, versus 34% (95) of non-HIV specialists ($p = .01$).

Similarly, in the second scenario, regarding procreative sex between a virologically suppressed HIV patient and his/her seronegative partner, 50% of the interviewed subjects stated that they esteemed zero risk of HIV transmission in this condition. In comparison, 22% still identified an ''extremely low'' level of risk in this condition.

Remarkably, an equal percentage of ID specialists (22%) chose the answer n. 3, declaring they would allow the possibility of unprotected procreative sex in serodiscordant couples, but would also advise PEP assumption to the HIV-negative partner.

Table 1. General Features of Survey Respondents

	Survey participants (N = *286*)	*HIV specialists* (N = *136*)	*Non-HIV specialists* (N = *150*)	p
Male sex, *n* (%)	135 (47)	62 (22)	71 (23)	.96
Age in years, median (q1–q3)	46 (34–58)	46 (34–59)	45 (34–58)	.83
Geographical position of center				
South Italy	85 (30)	40 (14)	45 (16)	.40
Middle Italy	56 (20)	31 (11)	25 (9)	
North Italy	145 (50)	65 (23)	80 (28)	
Working in a teaching hospital, *n* (%)	179 (63)	97 (34)	82 (29)	**.004**
HIV patients attending the center, median (q1–q3)	850 (600–1,300)	800 (650–1,250)	900 (580–1,400)	.83
Working as infectious diseases specialist, years, median, (q1–q3)	21 (21–33)	22 (9–33)	20 (9–32)	.60
Working as HIV specialist, years, median (q1–q3)	16 (16–27)	18 (8–28)	—	—

p values < .05 were marked in bold, as statistically significant.

Table 2. English Language Version of the Six-Item Survey Used in the Study

	Overall (N = 286)	Working in a teaching hospital: No (N = 107)	Working in a teaching hospital: Yes (N = 179)	p
Scenario 1: condomless sex				
Question: A virologically suppressed HIV-positive patient under effective treatment (tested within the last 2 months) asks you whether he/she can have sex without a condom. What would you answer?*				
1. Yes, because studies have confirmed that in your current condition the risk of sexual transmission is zero.	144 (50)	47 (15)	97 (35)	**.03**
2. Yes, because in your current condition the risk is extremely low.	60 (21)	18 (6)	42 (15)	
3. Yes, but your partner might consider taking prophylaxis with FTC/TDF.	19 (7)	7 (3)	12 (4)	
4. No, because you can't be sure that plasma HIV RNA is still undetectable on time of sex.	24 (8)	15 (5)	9 (3)	
5. No, because we need more data, before avoiding condom use.	16 (6)	9 (3)	7 (3)	
6. No, because it is safer to use condoms even when plasma HIV RNA is undetectable.	21 (8)	10 (4)	11 (4)	
*Two respondents did not provide any answer				
Scenario 2: procreative sex				
Question: A virologically suppressed HIV-positive patient under effective treatment (HIV RNA performed within the last 2 months) asks you whether he/she can have sex without a condom with his/her HIV-negative partner because they wish to have a baby. What would you answer?*				
1. Yes, because studies have confirmed that in your current condition the risk of sexual transmission is zero.	142 (50)	48 (17)	94 (33)	.09
2. Yes, because in your current condition the risk is extremely low.	63 (22)	21 (7)	42 (15)	
3. Yes, but your partner might consider taking prophylaxis with FTC/TDF.	64 (22)	30 (10)	34 (12)	
4. No, because you can't be sure that plasma HIV RNA is still undetectable on time of sex.	7 (2)	1 (0.5)	6 (2)	
5. No, because we need more data, before avoiding condom use.	5 (2)	4 (1)	1 (0.5)	
6. No, because it is safer to use condoms even when plasma HIV RNA is undetectable.	4 (2)	2 (1)	2 (1)	
*1 respondent did not provide any answer				
Scenario 3: occupational exposure				
Question: A health care worker, while drawing a blood sample from a virologically suppressed HIV-positive patient on therapy (HIV RNA performed in the last 2 months), reports accidental exposure through a skin prick. Would you recommend starting HIV postexposure prophylaxis?*				
1. No, because the risk of transmission is zero.	47 (17)	12 (4)	35 (13)	.46
2. No, because in this case, the risk is extremely low.	34 (12)	10 (3)	24 (9)	
3. No, but I would talk about the option of prophylaxis with FTC/TDF.	30 (11)	11 (4)	19 (7)	
4. No, but if the patient is more comfortable, he may start prophylaxis with FTC/TDF, waiting for a more recent patient's plasma HIV RNA test	61 (21)	23 (8)	38 (13)	
5. Yes, because we can't be sure that plasma HIV RNA is still undetectable on the day of the exposure.	67 (23)	30 (10)	37 (13)	
6. Yes, because we need more data before avoiding PEP in such cases.	25 (9)	10 (4)	15 (5)	
7. Yes, because it is always safer to take PEP.	21 (7)	10 (3)	11 (4)	
*1 respondent did not provide any answer				
Scenario 4: viral blip occurrence				
Question: An HIV-negative MSM reports a condom breaking during the last receptive anal intercourse with his HIV-positive partner who has been on stable and successful HAART for 5 consecutive years. However, despite an optimal self-reported adherence, the patient's last HIV RNA test (performed 2 weeks before) was 128 copies/mL. Would you recommend postexposure prophylaxis?*				
1. No, trials in serodiscordant couples were based on plasma HIV RNA being <200 copies/mL: the risk of transmission is zero.	67 (24)	17 (6)	50 (18)	**.03**
2. No, because in this case, the risk is extremely low.	12 (4)	1 (0.5)	11 (4)	
3. No, but I would prescribe PEP if the exposed partner feels more comfortable.	31 (11)	12 (4)	19 (7)	
4. Yes, because plasma HIV RNA could have been higher at the time of condom breaking.	112 (39)	46 (16)	66 (23)	
5. Yes: more data are needed before avoiding PEP in such cases.	38 (13)	18 (6)	20 (7)	
6. Yes, because it is always safer to take PEP.	25 (9)	12 (4)	13 (5)	
*1 respondent did not provide any answer				

(*continued*)

TABLE 2. (CONTINUED)

	Overall (N = 286)	Working in a teaching hospital: No (N = 107)	Working in a teaching hospital: Yes (N = 179)	p
Scenario 5: absence of recent HIV RNA test				
Question: A male patient on HAART reporting optimal adherence, presented persistently undetectable plasma HIV RNA over the last 3 years. He reports condomless vaginal intercourse with ejaculation with an HIV-negative woman. His last HIV RNA test (performed 6 months before) was undetectable. The lady asks you whether her partner is ''contagious or not.''				
How do you consider his last plasma HIV RNA test?*				
1. The test is reliable enough for this type of patient, PEP is not required.	105 (37)	39 (14)	66 (33)	.42
2. The test is too old, retesting is warranted. I would recommend PEP until an additional HIV RNA test is available.	152 (54)	53 (19)	99 (35)	
3. Time of testing is irrelevant; I would always suggest PEP to the HIV-negative partner as a safer approach.	27 (9)	13 (5)	14 (5)	
*2 respondents did not provide any answer				
Scenario 6: appropriate timing of HIV RNA testing				
Question: The infectious diseases specialist's recommendation on the risk of HIV sexual transmission in virologically suppressed patients is based on a plasma HIV RNA test (being or not undetectable). How long can the last HIV RNA test date back to be reliable in a clinical decision-making process?*				
1. One month before.	41 (15)	16 (6)	25 (9)	**.03**
2. Two months before.	28 (10)	7 (3)	21 (7)	
3. Three months before.	6 (2)	5 (2)	1 (0.5)	
4. Four months before.	2 (1)	2 (1)	0	
5. It always depends on the patient's pattern of adherence over time and his/her history of virological suppression.	208 (72)	76 (26)	132 (46)	
*1 respondent did not provide any answer				

p values < .05 were marked in bold, as statistically significant.

The frequency of answers collected for each question is reported. Pearson's χ^2 test/Fisher exact test was performed, as appropriate, to assess differences in answers provided by infectious diseases specialists working in teaching or nonteaching hospitals.

FTC/TDF, Tenofovir/FTC; HAART, highly active antiretroviral therapy; MSM, males who have sex with males; PEP, post exposure prophylaxis.

The third scenario addressed the issue of PEP prescription in the situation of occupational exposure (needle stick incident with an HIV-positive patient under therapy, but with the last HIV RNA test performed two months before): we detected contrasting clinicians' opinions in this case. We did not figure out a precise orientation for PEP prescription. We did not observe significant differences in the frequency of answers to this question between HIV specialists and non-HIV specialists and between providers working in teaching versus nonteaching hospitals.

A stronger orientation toward PEP prescription emerged from answers regarding Scenarios 4 and 5. We asked physicians whether they would advise PEP assumption for the HIV-negative partner in case of sexual intercourse with a seropositive patient with a recent blip occurrence (detectable viral load <200 copies/mL) (Scenario 4) or in case of sexual exposure with an HIV-positive patient with a long history of adherence to antiretroviral treatment but with no viral load documented in the last six months (Scenario 5).

More than 60% of interviewed specialists would advise PEP to the sexually exposed partner in Scenario 4, with higher proportions among specialists from teaching hospitals (99 subjects, 35% vs. 76 subjects, 26% of clinicians working in nonteaching hospitals, $p = .03$).

Concerning Scenario 5, more than 60% of subjects considered an HIV RNA test performed more than six months before to be not reliable enough for a clinical decision and agreed on the necessity of PEP prescription to the exposed subject until an updated viral load of the HIV-positive partner would be available.

Finally, the last scenario asked to identify the perfect schedule for HIV RNA testing.

Overall, 72% of the interviewed providers believed that knowing the patient's pattern of adherence and history of virological suppression is crucial for interpreting his/her HIV RNA test rather than simply the timing of the test itself. This opinion was more diffused among clinicians working in university hospitals (132 subjects, 46%) than those working in nonuniversity hospitals (76 subjects, 26%, $p = .03$).

Discussion

Spreading knowledge about the U = U concept is one of the significant tasks for HIV care providers today.

Increasing the awareness and the true meaning of this message among PLWH and the general public provides both individual and public health benefits. Among them, increasing patients' motivation to achieve and maintain viral suppression, reducing the anxiety about HIV acquisition among seronegative individuals, raising the willingness for HIV testing among people uncertain of their serostatus, and, ultimately, alleviating social and self-stigma that still burdens PLWH.[6,10]

The real challenge for clinicians comes when asked to transfer the known research data supporting U = U evidence[1,2] into real-life clinical decisions regarding situations at potential risk for sexual or occupational HIV transmission that could imply the prescription of PEP.

Table 3. English Language Version of the Six-Item Survey Used in the Study

	Overall, N = *286*	*HIV specialists*		
		No (N = *150)*	*Yes* (N = *136)*	p
Scenario 1: condomless sex				
Question: A virologically suppressed HIV-positive patient under effective treatment (tested within the last 2 months) asks you whether he/she can have sex without a condom. What would you answer?*				
1. Yes, because studies have confirmed that in your current condition the risk of sexual transmission is zero.	144 (50)	61 (21)	83 (30)	**.01**
2. Yes, because in your current condition the risk is extremely low.	60 (21)	34 (12)	26 (9)	
3. Yes, but your partner might consider taking prophylaxis with FTC/TDF.	19 (7)	12 (4)	7 (2)	
4. No, because you can't be sure that plasma HIV RNA is still undetectable on time of sex.	24 (8)	16 (6)	8 (3)	
5. No, because we need more data, before avoiding condom use.	16 (6)	13 (5)	3 (1)	
6. No, because it is safer to use condoms even when plasma HIV RNA is undetectable.	22 (8)	14 (5)	8 (3)	
**1 respondent did not provide any answer*				
Scenario 2: procreative sex				
Question: A virologically suppressed HIV-positive patient under effective treatment (HIV RNA performed within the last 2 months) asks you whether he/she can have sex without a condom with his/her HIV-negative partner because they wish to have a baby. What would you answer?				
1. Yes, because studies have confirmed that in your current condition the risk of sexual transmission is zero.	142 (50)	63 (22)	79 (28)	.14
2. Yes, because in your current condition the risk is extremely low.	63 (22)	36 (13)	27 (9)	
3. Yes, but your partner might consider taking prophylaxis with FTC/TDF.	64 (22)	40 (14)	24 (8)	
4. No, because you can't be sure that plasma HIV RNA is still undetectable on time of sex.	7 (2)	5 (2)	2 (1)	
5. No, because we need more data, before avoiding condom use.	5 (2)	3 (1)	2 (1)	
6. No, because it is safer to use condoms even when plasma HIV RNA is undetectable.	5 (2)	3 (1)	2 (1)	
Scenario 3: occupational exposure				
Question: A health care worker, while drawing a blood sample from a virologically suppressed HIV-positive patient on therapy (HIV RNA performed in the last 2 months), reports accidental exposure through a skin prick. Would you recommend starting HIV postexposure prophylaxis?				
1. No, because the risk of transmission is zero.	47 (16)	23 (8)	24 (8)	.19
2. No, because in this case, the risk is extremely low.	34 (12)	22 (8)	12 (4)	
3. No, but I would talk about the option of prophylaxis with FTC/TDF.	30 (10)	18 (6)	12 (4)	
4. No, but if the patient is more comfortable, he may start prophylaxis with FTC/TDF, waiting for a more recent patient's plasma HIV RNA test.	61 (21)	29 (10)	32 (11)	
5. Yes, because we can't be sure that plasma HIV RNA is still undetectable on the day of the exposure.	67 (24)	36 (13)	31 (11)	
6. Yes, because we need more data before avoiding PEP* in such cases.	25 (9)	8 (3)	17 (6)	
7. Yes, because it is always safer to take PEP.	22 (8)	14 (5)	8 (3)	
Scenario 4: viral blip occurrence				
Question: An HIV-negative MSM reports a condom breaking during the last receptive anal intercourse with his HIV-positive partner who has been on stable and successful HAART for 5 consecutive years. However, despite an optimal self-reported adherence, the patient's last HIV RNA test (performed 2 weeks before) was 128 copies/mL. Would you recommend postexposure prophylaxis?				
1. No, trials in serodiscordant couples were based on plasma HIV RNA being <200 copies/mL: the risk of transmission is zero.	67 (23)	34 (12)	33 (11)	.50
2. No, because in this case, the risk is extremely low.	12 (4)	5 (2)	7 (2)	
3. No, but I would prescribe PEP if the exposed partner feels more comfortable.	31 (11)	18 (6)	13 (5)	
4. Yes, because plasma HIV RNA could have been higher at the time of condom breaking.	112 (39)	56 (20)	56 (19)	
5. Yes: more data are needed before avoiding PEP in such cases.	38 (14)	19 (7)	19 (7)	
6. Yes, because it is always safer to take PEP.	26 (9)	18 (6)	8 (3)	
Scenario 5: absence of recent HIV RNA test				
Question: A male patient on HAART reporting optimal adherence, presented persistently undetectable plasma HIV RNA over the last three years. He reports condomless vaginal intercourse with ejaculation with an HIV-negative woman. His last HIV RNA test (performed 6 months before) was undetectable. The lady asks you whether her partner is ''contagious or not.''				

(*continued*)

TABLE 3. (CONTINUED)

	Overall, N = *286*	*HIV specialists*		
		No (N = *150)*	*Yes* (N = *136)*	p
How do you consider his last plasma HIV RNA test?				
1. The test is reliable enough for this type of patient, PEP is not required.	105 (37)	49 (17)	56 (20)	.20
2. The test is too old, retesting is warranted. I would recommend PEP until an additional HIV RNA test is available.	152 (53)	83 (29)	69 (24)	
3. Time of testing is irrelevant; I would always suggest PEP to the HIV-negative partner as a safer approach.	28 (10)	18 (69	10 (3)	
Scenario 6: appropriate timing of HIV RNA testing				
Question: The infectious diseases specialist's recommendation on the risk of HIV sexual transmission in virologically suppressed patients is based on a plasma HIV RNA test (being or not undetectable). How long can the last HIV RNA test date back to be reliable in a clinical decision-making process?*				
1. One month before.	42 (15)	22 (8)	20 (7)	.90
2. Two months before.	28 (10)	13 (4)	15 (5)	
3. Three months before.	6 (2)	4 (1)	2 (1)	
4. Four months before.	2 (1)	1 (0.5)	1 (0.5)	
5. It always depends on the patient's pattern of adherence over time and his/her history of virological suppression.	208 (72)	11 (38)	98 (34)	
**1 respondent did not provide any answer*				

p values < .05 were marked in bold, as statistically significant.
The frequency of answers collected for each question is reported. Pearson's χ^2 test/Fisher exact test was performed, as appropriate, to assess differences in answers provided by HIV and non-HIV specialists.

This survey attempted to collect, for the first time in Italy, perceptions of ID specialists about the risk of HIV transmission between virologically suppressed patients and seronegative individuals, both in the sexual and occupational context of exposure, and to understand the recommendations that clinicians are currently providing for PEP in complex real-life situations at potential risk for HIV transmission.

We voluntarily addressed these interviews to experienced clinicians working in the Italian centers of ID chosen as having long-standing expertise in HIV treatment: respondents reported having a median of a 20-year experience in the field of ID. Under half of the population mainly focused their careers on managing HIV infection.

The proposed questionnaire included six clinical scenarios involving HIV-positive subjects under effective antiretroviral treatment: we asked providers to express their clinical decisions not only about ordinary circumstances of possible exposure but especially in complex borderline situations requiring an evaluation of the need for PEP prescription as well. Among them, a case of sexual contact occurred with an HIV-positive patient who (1) reported a recent viral blip, (2) lacked a recent HIV RNA test, or (3) for whom information regarding the pattern of adherence and the history of viral suppression was unavailable or an episode of occupational exposure with a seropositive patient under therapy but with no recent HIV RNA test available.

We observed that the more significant part of participants esteemed no risk for HIV transmission, thus demonstrating knowledge and application of the U = U equation, when questioned regarding everyday situations of sexual exposure, that is, condomless sex between an HIV-positive, virologically suppressed subject tested within the last 2 months and his/her seronegative partner.

Nevertheless, a significant percentage of responders affirmed that in the up-mentioned context, the transmission risk is, rather than zero, ''extremely low.''

British HIV Association (BHIVA) members responded to a similar anonymous online survey in October 2018.[7] Surprisingly, only 20% of the 270 respondents reported hearing about the U = U message from colleagues. Moreover, only 37% of clinicians were explicit with their patients about U = U having a zero risk, while primarily using other less-direct words, such as ''extremely low,'' next to zero, virtually impossible, or negligible, similarly to what was observed in the present survey.

The use of the expressions ''extremely low risk'' (a recurrent expression in antiretroviral Italian guidelines[9]) and ''zero risk'' conveys a sense of uncertainty to the patient's direct question (and, more broadly, to the public), being more than just semantic. It suggests that, despite robust clinical data, the provider is not fully confident in U = U.

In light of these considerations, BHIVA has recommended using ''consistent and unambiguous terminology'' (i.e., zero risk) as other expressions are not helpful in terms of public health messaging.

Surprisingly, a small but significant number of providers proposed PEP for the exposed partner, despite undetectable viral load in the seropositive subject. Uncertainties, in this case, were motivated by the absence of an updated HIV RNA test at the time of sexual intercourse, the unavailability of robust epidemiological data, or by the possibility of persistent risk of HIV transmission without a condom even in virologically suppressed patients and often led the clinician to a ''wait-and-see'' approach that also included PEP prescription.

We would also underline that a significant difference was observed between opinions collected regarding this point by clinicians from university centers or having broader expertise in the HIV field and their counterparts.

This observation suggests that a more robust clinical experience in HIV management can affect the knowledge and confidence in the concept of absence of risk for virologically

suppressed individuals to transmit HIV and that this theory needs to be reinforced first among ID specialists before being diffused to the broader community.

More cautious attitudes and more considerable uncertainties were detected among clinicians when called to apply scientific evidence about U = U to the clinical decisions in more complex scenarios of exposure, potentially requiring the assumption of PEP for the exposed partner.

A possible explanation of this evidence could be the absence of a clear indication from national and international guidelines, which often express ambiguous and contrasting suggestions, providing little help in guiding clinical decisions.

Regarding condomless sex, the Italian guidelines report the results from the Partner and Opposite Attract studies,[2,11] but do not provide a clear recommendation on PEP prescription. On the contrary, the European HIV Treatment guidelines[12] state that in case of documented undetectable plasma HIV-RNA, PEP is no longer recommended in an HIV-negative partner, while in case of sexual exposure with an HIV-positive partner, PEP should always be started and discontinued after the confirmation of an undetectable HIV RNA. The timing of the last HIV RNA is never mentioned.

With regard to risk evaluation about procreative sex, the Italian guidelines state that, for occupational exposure, no PEP is required (although the clinician can prescribe it pending the HIV RNA documentation). Conversely, the European HIV Treatment guidelines[12] recommend PEP for occupational exposure to blood if the source subject is HIV positive.

Finally, the Italian guidelines target the issue of pregnancy, but make no mention of the safety of condomless intercourse in the setting of procreative sex: they recommend testing HIV RNA every three months in HIV women whose partner is on effective therapy, but the absence HIV transmission risk in this context is never clearly stated.[9]

Consequently, divergent views and an overall cautious attitude were observed among the Italian ID providers when called to translate the U = U message into daily clinical decisions.

Regarding the event of sexual exposure with a seropositive subject with a recent viral blip occurrence, providers showed uncertainty on the absence of risk of HIV transmission.

The possibility of a higher plasmatic HIV viral load on the day of exposure compared with the last test was a significant driver of this response. Not having low viremia (as low as 128 copies/mL) reduced the specialist's concern, even if both the PARTNER[1,2] and Opposite Attract[11] trials used an HIV RNA threshold below 200 copies/mL for the definition of undetectable.

We did not outline explicit agreement among providers or concerting the appropriate timing of HIV RNA testing that could ease clinical decisions regarding potential PEP prescription. From the answers collected, clinicians would advise more intensive HIV RNA monitoring in stable virologically suppressed patients.

Unfortunately, due to the advent of the SARS-CoV-2 pandemic, the management of HIV infection has changed, and clinical choices are frequently taken in the absence of a recent HIV RNA test.

Hopefully, most of the interviewed subjects agreed that, beyond HIV RNA, they need more clinical data regarding the pattern of adherence of the patient for a proper evaluation of the need for PEP for the exposed subject after sexual/occupational contact.

This information could compensate for the lack of recent virological data and allow us to avoid PEP in the case of PLWH with a history of solid adherence to antiretroviral therapy and long-time viral suppression.

In this view, a reinterpretation of the U = U concept appears more ''patient related'' than ''viremia related.''

Our study has some limitations.

First, the questionnaire tool proposed has been self-developed by coauthors because no validated survey exists that could fit this study's aim.

Moreover, the internal validation process of the survey has not included the distribution of the questionnaire to a control group (i.e., non-ID specialists), as questions specifically addressed ID providers and topics related to the management of situations hazardous for HIV transmission.

Face validity and internal consistency have been assessed by performing accompanied pilot interviews on a small number of respondents, as explained in the Methods section, but the survey does not follow a validated scale.

Moreover, due to this survey's nature (anonymous, self-compiled, and filled voluntarily), it was impossible to precisely establish the attendance rate, as we did not record the proportion of clinicians refusing to participate.

The second major limitation was that we did not calculate the sample size for this survey, but we set a two-month time frame (from May 1 to June 30, 2019), during which all providers in centers enrolled in the Real-Time Study Group would have received and potentially compiled the questionnaire.

Lastly, our questionnaire was available only in the Italian language and was addressed only to the ID centers belonging to the ''Real-Time Study Group'': results should therefore be cautiously interpreted as not representative of the situation in the Italian countryside. We wish to underline that we intentionally did not consider these conditions in the questionnaire as they would have further complicated the decision-making process for PEP prescription, as the concomitant suspected or diagnosed presence of sexually transmitted diseases or the achievement of virological suppression in patients on dual regimens. To this aim, a wider diffusion of similar surveys is advisable.

Nevertheless, these data highlight that much work is left to do for ID specialists to increase the knowledge of the real meaning of the U = U message, which should be based on the individual clinical and immune-virological history of the patient, besides the mere virological data.

Only in this way could the message be spread to clinicians of other medical specialties and the wider community, finally contributing to overcoming the feeling of stigma that surrounds decades of HIV infection and PLWH.

Conclusions

A significant percentage of the Italian ID specialists showed a lack of confidence in the absence of risk in case of sexual exposure with HIV-positive, virologically suppressed individuals. We mainly detected uncertainties among clinicians working in nonuniversity hospitals and not primarily involved in the field of HIV and were referred mainly to the timing of the last HIV RNA to the exposure event.

Such clinical doubts, understandably, could also affect the other clinical scenarios where the risk estimation is more complex because specific guidelines' indications/trial data are lacking.

More clarity and consistency are warranted by national and international HIV guidelines about PEP prescription in case of condomless sex with subjects with undetectable HIV plasma RNA. Moreover, topics such as PEP prescription in the event of occupational exposure, PreExposure Prophylaxis advice for the HIV-negative partner in the case of procreating sex, and, lastly, correct timing of HIV RNA testing should be clarified to help clinicians make firm decisions and give firm answers to their patients.

We should all work to implement the education strategy to support the U = U message and efficiently translate the new concept into reality. The process should start with ID specialists in the front line of HIV care.

Authors' Contributions

D.R. and S.L.C.: conceptualization, methodology, writing (original draft), and supervision; M.P. formal analysis, writing (review and editing), and visualization; G.Maz., P.C., A.D.B., B.M.C., A.G., R.B., G.Mad., S.N., and S.R.: resources, investigation, data curation, and writing (review and editing); S.L.C.: project administration.

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References

1. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. J Am Med Assoc 2016; 12;316(2):171–181; doi: 10.1001/jama.2016.5148
2. Rodger AJ, Cambiano V, Bruun T, et al. Study Group al. Risk of HIV transmission through condomless sex in sero different gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): Final results of a multicentre, prospective, observational study. Lancet 2019;393(10189):2428–2438; doi: 10.1016/S0140-6736(19)30418-0.
3. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. N Engl J Med 2016;375(9):830–839; doi: 10.1056/NEJMoa1600693
4. Eshleman SH, Hudelson SE, Redd AD, et al. Treatment as prevention: Characterization of partner infections in the HIV Prevention Trials Network 052 Trial. J Acquir Immune Defic Syndrome 2017;74(1):112–116; doi: 10.1097/QAI.0000000000001158
5. Prevention Access Campaign. Consensus statement. 2019. Risk of sexual transmission of HIV from a person living with HIV who has an undetectable viral load. Available from: https://www.preventionaccess.org/consensus [Last accessed: April 14, 2022].
6. Calabrese SK, Mayer KH. Providers should discuss U = U with all patients living with HIV. Lancet HIV 2019;6(4): e211–e213; doi: 10.1016/S2352-3018(19)30030-X
7. Gupta N. 2019 BHIVA Pre-conference Meeting: Important Challenges. BHIVA's position on U = U an update. Available from: https://www.bhiva.org/AnnualConference2019 Presentations [Last accessed: April 14, 2022].
8. Report of healthcare professionals in Italy, 2020. Available from: www.pkegroup.it/html/blog/infettivologi-in-italia-quanti-sono-e-dove-lavorano.asp [Last accessed: June 19, 2021].
9. Italian Guidelines for the Use of Antiretroviral Agents. Edition 2017. Available from: www.salute.gov.it/imgs/C_17_pubblicazioni_2696_allegato.pdf [Last accessed: April 14, 2022].
10. Bruno SR, Poliseno M, Vichi F, et al. General Practitioners as partners for a shared management of chronic HIV infection: An insight into the perspectives of Italian People Living with HIV. PLoS One 2021;16(7):e0254404; doi: 10.1371/journal.pone.0254404
11. Bavinton BR, Jin F, Prestage G, et al. The Opposites Attract Study of viral load, HIV treatment and HIV transmission in serodiscordant homosexual male couples: Design and methods. BMC Public Health 2014;14:917; doi: 10.1186/1471-2458-14-917
12. European AIDS Clinical Society. Treatment guidelines. 2021. Version 11.0. Available from: https://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html [Last accessed: April 14, 2022].

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