



## Undetectable HIV Equals Untransmittable HIV (U = U) Statement in Women. Are we there Yet?

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### Abstract

**Introduction:** The “undetectable equals untransmittable” (U = U) statement confirms that a HIV positive person on effective antiretroviral therapy is not transmitting HIV to his/her sexual partner. Poor adherence to treatment can jeopardize this benefit. Women living with HIV (WLWH) are more at risk of having suboptimal adherence than men.

**Objectives:** To compare the characteristics of women on effective cART with those who have a detectable HIV viral load (VL), in order to understand the differences in behavioral patterns and to better address the U = U statement among women.

**Methods:** Women with HIV using gynecological services in the Out-Patient Clinic in Warsaw participated in a survey about sexual behavioral patterns and history of sexually transmitted infections (STIs). The data about HIV VL, status of HCV, HPV and other STIs was exported from the medical database. Characteristics of women with HIV RNA>50 copies/ml and women with HIV RNA<50 copies/ml were compared using non-parametric tests as appropriate.

**Results:** The study included 97 WLWH with median age 39 years and 82 (84.5%) with undetectable HIV VL. The median number of sexual partners in both groups was five (IQR: 3.5-8.5 and 3-10 for those with VL<50 and VL>50 respectively). Most characteristics were comparable between study groups except that more women with detectable VL did not use condoms (66.7% vs. 39%, p = 0.0244).

**Conclusions:** More attention should be drawn to reasons of poor adherence to cART in WLWH. Same efforts in educating about safe sex and U = U should be made in WLWH as for other key populations.

**Keywords:** HIV; cART; Undetectable; Untransmittable; Adherence; Women

### Introduction

The early treatment of HIV-positive patients together with the “undetectable equals untransmittable” (U = U) global consensus are important parts of strategies of HIV prevention worldwide [1,2]. However, the ability of combined antiretroviral therapy

(cART) to suppress viral replication depends on adherence to these medications. Many factors such as stigma, depression, side effects of medication can contribute to decrease of adherence [3-5]. Studies show that women living with HIV (WLWH) are more at risk of having suboptimal adherence than men, especially after pregnancies or

during menopause [6-10]. Meanwhile as they are sexually active, they might acquire other sexually transmitted infections (STIs) and thus have an increased risk of HIV transmission [11].

The objective of this study was to compare the characteristics of women with effective cART defined as HIV viral load (VL) below 50 copies/ml with those who have a detectable HIV VL, thus suboptimal adherence, in order to understand the differences in behavioral patterns of these groups, and to better address the U = U statement among women.

## Material and Methods

All WLWH being under the care of the HIV Out-Patient Clinic in Warsaw were eligible for the study. All women who consented to participate in the study filled in a study questionnaire focusing on sexual behavioral patterns, history of STIs, partner HIV status. Data on cART and the most recent laboratory values were extracted from the electronic medical database. In terms of laboratory methods for HIV RNA Abbott Real Time HIV-1 test was used, for HCV RNA Abbott Real Time HCV test and for HPV DNA the HPV Genotypes 14 Real-TM Quant kit were used. Moreover, the infection of *C. trachomatis* and *N. gonorrhoea* were detected by Gene Xpert CT/NG test (cervicovaginal lavage) and syphilis was diagnosed by the RPR Carbon Latex test (blood serum).

In statistical analyses the characteristics of women with HIV RNA >50 copies/ml and women with HIV RNA <50 copies/ml were compared using non-parametric tests as appropriate. All tests of significance were two-sided and type I error rate was 5%. A confidence interval (CI) of 95% was accepted. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). The study obtained approval from the Bioethical Committee of the Medical University of Warsaw.

## Results

The study included 97 WLWH with median age 39 (IQR: 35-45) years. Out of the 97 patients 82 (84.5%) were infected with HIV through heterosexual contacts, 13 (12.6%) through intravenous drug usage (IDU). The patients had a median of 10 (IQR: 3-15) years in HIV care and had a median of 598 CD4 (IQR: 404-760) cells/ $\mu$ l. All women claimed to be on cART but 15 of them had detectable VL with a median of 23 931 (IQR: 4 013-83 587) copies/ml. Six of these (40%) had suboptimal adherence, one of them took

cART only during pregnancies. The most commonly used cART regimen was boosted protease inhibitors 45 (46.3%) and integrase inhibitors-based 39 (40.2%).

Thirty-one (32%) patients had a HIV positive partner, ten (10.3%) did not know the HIV status of their partner and four of these women had a detectable VL. Two women did not answer to this question, but they had an undetectable VL. The rest (n = 54, 56%) had a partner without HIV and four of these women had a detectable viral load.

The same percentage of women in both groups declared being in a stable relationship (p = 0.206). The number of sexual partners per participant of the survey did not differ much between women with detectable and undetectable VL (median in both groups was 5 partners). Twenty-five percent of women with undetectable viral load had more than 10 sexual partners, and 25% of women with detectable viral had more than 7 sexual partners. Women with detectable viral load were statistically significantly less often using condoms (66.7%) than women with undetectable viral load (39%), (p = 0.0244). Thirty women responded that they either use condoms "sometimes" or "often". There was no statistically significant difference between type of sexual behavioral or its pattern between these two groups. Similar numbers of women in both groups declared having oral and/or anal sex. Data on sexual behavioral patterns, use of condoms, partner HIV status of participants are shown in table 1.

Out of the 97 women 45 (46.4%) were HPV positive, with a greater prevalence in the group of patients with detectable viral load in comparison with those with undetectable viral load (73.3% vs. 41.5%, p = 0.0194). HCV RNA was positive in both groups with similar frequency (32.9% vs. 20%; p = 0.148). Data on the prevalence of HPV and HCV is shown in table 1. Four patients had another STI (chlamydia, gonorrhoea, HSV or syphilis) and all of these patients had an undetectable viral load.

## Discussion

Many studies have demonstrated that early initiation of antiretroviral therapy reduces rates of sexual transmission of HIV [1,12]. Based on the studies, the international recommendations about HIV treatment have been changed to starting cART at

		VL<50 copies/ml N = 82	VL>50 copies/ml N = 15	p-value
Nr of sexual partners ever, median (IQR)		5 (3-10)	5 (3-10)	0.784
Nr of sexual partners (last 3 months) median (IQR)		1 (0-1)	1 (0-1)	0.223
Condoms n(%)	Always	22 (26.8)	3 (33.3)	0.0244
	Never	32 (39)	10 (66.7)	
	Sometimes	22 (26.8)	2 (13.3)	
	Often	6 (7.3)	0	
Oral sex n(%)		27 (32.9)	4 (26.6)	0.218
Anal sex n(%)		11 (13.4)	2 (13.3)	0.315
In stable relation n(%)		48 (58.5)	8 (53.3)	0.206
Partner HIV-positive, n(%)		25 (30.4)	7 (46.6)	0.036
HCV RNA positive n(%)		27 (32.9)	3 (20)	0.148
HPV DNA positive n(%)		34 (41.5)	11 (73.3)	0.0194

**Table 1:** Characteristics of sexual behavioral patterns, use of condoms, partner HIV status of women participating in the study.

the time of HIV diagnosis and irrespectively of CD4 cell count. The “treatment as prevention” (TasP) has become basis of HIV prevention strategies worldwide. Following the large studies carried out between 2007 and 2016 among serodiscordant couples it was demonstrated that condomless sex did not result in HIV transmission if the HIV-positive partner was using suppressive cART [1,13,14]. But for the “undetectable to equal untransmittable” (U = U) adherence plays a crucial role.

So far, only 59% of people living with HIV worldwide have undetectable levels of the virus [15]. In Poland it has been shown that over 90% of patients on cART are virologically suppressed. But when we analyze these data separately for women and men, we can see that in Poland less women than men have achieved undetectable viral load <50 copies/ml (89,25% vs. 91,02% for women and men respectively) [16].

In our study, which analyzed only women, 84% of participants had undetectable viral load (<50 copies/ml). Over 15% of women had detectable viral load but only six of these patients declared suboptimal adherence. Moreover, women with detectable VL were more likely not to use condoms during sex. In a study by Okoli, *et al.* 66.5% of 2389 PLVH participating in the survey reported ever discussing U = U with their healthcare provider. Those who

discussed the U = U statement had lower odds of suboptimal adherence and detectable viral load [17]. It is important that the patient is not only aware of the medical consequences of non-adherence but is also aware of the motivations for non-adherence. Naming the reasons of non-adherence might allow the medical personnel to help the patient to improve the adherence.

In 2019 of 38 million people living with HIV 19,2 million were women (51%). Even though globally more women than men are receiving antiretroviral treatment (73 vs. 61%) women have lower adherence rates of cART than men [6,7]. In fact, women were identified as hard to reach population at each continuum of care in Central and South Eastern Europe [18]. There are many reasons for non-adherence and they change with time. Literature divides nonadherence to “intentional” and “unintentional” [19]. “Simply forgetting” remains one of the most frequently stated reasons of nonadherence [3,20,21]. Among other reasons of nonadherence Okonsky, *et al.* identified: “problems taking pills at a specified time”, “too busy with other things”. Stigma around HIV is still an important factor for suboptimal adherence of cART and engagement in medical care among WLWH [22]. More gender specific reasons for non-adherence include pregnancies, severe menopausal symptoms and depression [9,10,23]. More attention should be drawn to diagnosing and treating menopause in WLWH.

Recent studies demonstrate that menopause can appear earlier in women living with HIV than in women without HIV [24]. The cooperation between gynecologists and infectious diseases specialists is crucial, especially in the time of pregnancy, post-partum and menopause of a female patient with HIV.

Recently with less side effects of antiretroviral medication, “wanting to avoid side effects” is less frequently an explanation of nonadherence. Heroin use, once a popular factor associated with worse adherence among women, is now less of an issue. Many studies have shown that single tablet regimens (STRs) are associated with higher adherence to antiretroviral treatment [25].

In our study the median number of sexual partners in both groups was five, but the number of sexual partners in last three months was much lower. There is no data about the median number of sexual partners in Polish women without HIV. Education about safe sex is a crucial element of HIV prevention strategy. The fact that in our study women with detectable viral load were less often using condoms than women with undetectable VL (26.8%) may reflect the underestimation of the significance of the statement about U = U among women. This may reflect lesser efforts in informing WLWH on U = U statement than other patient groups. Same education efforts should be taken for WLWH as they are for men having sex with men. It is important to note that only one woman was infected with *Chlamydia trachomatis*. This correlates well with low number of sexual partners in a lifetime and with our earlier findings and indicates that most WLWH are in stable relationship [26]. In terms of cervical cancer prophylaxis, in our study all women had both the HPV screening and cytology done, and almost half (46.4%) of all participants tested HPV-positive which reminds us that HIV positive women are at increased risk of HPV acquisition and therefore should be regularly screened. As mentioned in our earlier work, barriers to cancer screening still exist and gynaecological care should be integrated into the HIV care [27].

There are important limitations of this study which need to be mentioned. First of all, our study had a small sample size. Secondly, we cannot control for selection bias, as only women using gynecological services were included in this study. As women consulted both by gynaecologist and HIV clinician might have better education, we could underestimate the number of women unaware

of the relation between VL and sexual behaviours. Finally, we were not able to compare our findings with general Polish population.

## Conclusions

Women living with HIV lead an active sex life with both HIV-positive and HIV-negative partners. Our study shows that the majority of sexual behaviours of women with detectable VL do not differ much from that of the women with undetectable VL (similar number of sexual partners, similar type of sexual act). But an important difference is that women with detectable VL were more likely not to use condoms during sex. The poor adherence to cART and lack of use of condoms can pose a risk of HIV transmission. More attention should be drawn to reasons of poor adherence to cART in WLWH. Reducing HIV-related stigma is an important element of achieving viral suppression. Early detection and treatment of depression and severe menopause symptoms might lead to improvement of adherence of cART. Same efforts in educating about safe sex and about U = U should be made in WLWH as they are in key populations. Where possible and feasible the gynecological services should be integrated in the HIV care of women.

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