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# Differential Influence of Different Hepatitis Viruses on Quality of Life in HIV Positive Patients

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**Abstract**
HIV-infected individuals are frequently co-infected with different hepatitis viruses. HCV has been associated with impaired quality of life in non-HIV infected patients. Little is known concerning the quality of life in HIV-infected individuals in relation to the different viral co-infections.
*Patients and Methods:* We investigated 250 patients who have answered "HIV-SELT" and EuroQoL ("EQ-5D") questionnaires assessing quality of life. Data on HBsAg, anti-HBc, anti-HCV, and GBV-C-RNA were available for 191, 188, 189, 98 patients, respectively. HCV-RNA was tested in 33 of 35 anti-HCV positive patients.
*Results:* There was no difference in quality of life in relation to active or past HBV-infection defined by HBsAg (n = 15) and anti-HBc in the absence of HBsAg (n = 84), respectively, for both overall HIV-SELT (p = 0.66, and p = 0.43, respectively) and visual "EQ-5D" (p = 0.93 and p = 0.64, respectively). However, anti-HCV positivity (n = 35) was associated with significantly impaired quality of life (HIV-SELT overall p<0.001). Importantly, no difference was found in relation to HCV-viraemia in anti-HCV positive patients (p = 0.77). In multivariate analysis anti-HCV positivity, employment status, HIV viral load and GBV-C were relevant to quality of life, with GBV-C being beneficial and HCV being negative.
*Conclusions:* While HBV seems to play no role concerning quality of live in HIV-infected patients, the flavi-viruses HCV and GBV-C display opposing influence on quality of life. As quality of life was similarly impaired in HCV-viraemic and HCV-non-viraemic anti-HCV positive patients but better in GBV-C viraemic patients, this should be taken into account in the indication case of planned interferon therapy.

*Key words:* HIV, HCV, hepatitis C, HBV, hepatitis B, GBV-C, Quality of life

## Introduction

The flavivirus GB Virus C [1, 2] has been linked to better survival in HIV-positive patients [3, 4, 5], while the closely related flavivirus, hepatitis C virus (HCV) [6, 7], as well as the hepatitis B virus (HBV) were linked to an impaired survival in the pre-HAART era [8, 9]. In the Post-HAART era, survival has still been reported to be severely impaired in hepatitis B virus (HBV) infected patients, while there was only moderate increased overall mortality observed in the HCV positive patients vs. the HCV negative patients within the EUROSIDA cohort [10].

Hepatitis C virus has frequently been associated with an impaired quality of life (QoL) in immunocompetent patients [11], but only few studies have looked into the relevance of HCV in relation to QoL in HIV positive patients, and furthermore, we are not aware of any study evaluating the role of present and past HBV-co-infection on QoL in HIV-positive patients.

Thus, it is of great interest to evaluate the differential influence the two hepatitis viruses, HCV and HBV, have on QoL in HIV positive patients, where two disease specific instruments have been validated in German language, the "HIV-SELT" [12] and the MOS-HIV [13].

We performed a study on QoL in HIV-positive patients, whose QoL was previously assessed in relation to GBV-C [14]. After determining HCV and HBV status, we now report on QoL in relation to hepatitis virus infections in this cohort of HIV positive patients.

## Patients and Methods

250 HIV-positive patients answered two questionnaires ("HIV-SELT"[12] and the "EQ-5D"[15]) concerning their health related QoL and their well being in 1997/1998. These two questionnaires were utilized, because they were validated instruments for HIV infected patients in the German language and which we had used before.

Patients transmission risks for HIV-infection were MSM (men who have sex with men: 56.4%), IVDU: (intravenous drug use 14.4%), hemophilia (3.6%), contaminated blood transfusion (1.6%), heterosexual exposure (13.2%), origin from endemic regions (2.8%), maternal transmission (0.8%) and unknown in 7.2%. There was a male dominance 82.4% (206/250), 110 of the patients were employed, mean values for age, HIV-viral load and CD4 cells were, 40,4 ± 10.6 years, 328.9 ± 215.4 cells, and 34234 ± 98438 Copies/mL.

The short version of "Scales for Examining Life Quality" (HIV-SELT) is comprised of 29 questions

(items) concerning six different dimensions (subscales) related to "Quality of Life". A higher score indicates a better health or better quality of life. In "EQ-5D", patients are asked to answer 5 questions in addition to rating their perception of their health on a visual analogue scale (VAS) from 0 to 100, where "0" is the worst and "100" is the best imaginable health. For interpretation it is important to note that lower counts indicate better health for the 5 dimensions, while higher counts indicate better health for the rating on the VAS. In addition to the self reported quality of life, the EQ-5D provides a community weighted index value (Health Index) based on the VAS method [16]. Statistical calculations were performed using SPSS 11.0. Differences between groups were calculated by the chi-square test or Fisher's exact test for categorical parameters and by the Wilcoxon's rank sum test for continuous parameters as these variable were not normally distributed. IQR are given for the results anti-HCV positive vs. anti-HCV negative. In addition, a regression analysis was performed to identify the relevant parameters in relation to quality of live for both HIV-SELT and EQ-5D. The mutlivariate linear regression, included age, anti-HBc, anti-HCV, HBsAg status, HIV-viral load, CD4 cell count, CDC stage of HIV disease, and durations since diagnosis of HIV infection, as well as GBV-status in a second analysis.

Age, CD4 count, HIV-viral load, duration since diagnosis of HIV infection were used as continues variables, HIV was initially not log transformed, but log transforming HIV viral load did not change the overall data.

QoL in 98 patients with known GBV-C vireamia status have previously been reported.[12] Here we now extended the analysis to include data on both HBV and HCV in relation to both HIV and GBV-C. HBsAg, anti HBc, anti-HCV, and HCV-RNA were tested by commercially available assays. Data on HBsAg, anti-HBc, anti-HCV, and GBV-C-RNA were available for 191, 188, 189, 98 patients, respectively. HCV-RNA was tested in 33 of 35 anti-HCV positive patients. While patients were not aware of the GBV-C status when questioned, they were aware about their hepatitis status concerning HBsAg and anti-HCV.

## RESULTS

HBsAg and anti-HBc data were available in 191 patients and were positive for 15 and 99 patients, respectively. Thus, 15 (7.9%) had active HBV co-infection and 84 (44.0%) had past HBV infection. Neither active nor past infection correlated with an impaired QoL in any of the categories. (Table 1)

This is in dramatic contrast to HCV co-infection, in which the 35 anti-HCV positive patients showed sig-

*Table 1.* Quality of Life in HIV Positive Patients Determined by EQ-5D and HIV-SELT in Relation to ongoing (A) or past (B) HBV-infection*.

| **A** | | HBsAg +, n = 15<br>mean ± SD; (median) | HBsAg -, n = 176<br>mean ± SD; (median) | p value # |
|---|---|---|---|---|
| EQ-5D | Visual Analogue Scale (VAS) | 69.9 ± 18.6; (75.0) | 68.6 ± 20.7; (75.0) | 0.96 |
| HIV-SELT | Actual mood | 79.0 ± 23.3; (83.1) | 70.5 ± 23,7; (75) | 0.13 |
| | Physical impairments | 59.0 ± 22.1; (54.1) | 64.2 ± 21.3; (65.9) | 0.33 |
| | Subjective feeling | 55.0 ± 25.1; (58.3) | 57.9 ± 26.5; (58.3) | 0.63 |
| | Basic mood | 68.2 ± 23.9; (79.2) | 64.8 ± 23.5; (70.8) | 0.45 |
| | Social support | 72.4 ± 21.2; (75) | 70.7 ± 22.7; (75) | 0.84 |
| | Life orientation | 63.3 ± 17.4; (58.3) | 55.1 ± 27.2; (58.3) | 0.31 |
| | Total score | 66.2 ± 17.2; (70.8) | 63.9 ± 18.5; (67.5) | 0.66 |
| **B** | | Anti-HBc +*, n = 84<br>mean ± SD; (median) | Anti-HBc -, n = 90<br>mean ± SD; (median) | p value # |
| EQ-5D | Visual Analogue Scale (VAS) | 67.6 ± 22.0; (70.0) | 69.4 ± 19.7; (75.0) | 0.64 |
| HIV-SELT | Actual mood | 68.7 ± 25.6; (73.4) | 71.9 ± 21.8; (75.0) | 0.61 |
| | Physical impairments | 62.9 ± 22.8; (62.5) | 65.3 ± 19.8; (68.8) | 0.53 |
| | Subjective feeling | 56.2 ± 27.1; (58.3) | 59.3 ± 26.0; (66.7) | 0.37 |
| | Basic mood | 63.8 ± 24.3; (70.8) | 66.0 ± 23.1; (70.8) | 0.67 |
| | Social support | 68.5 ± 22.4; (75.9) | 72.7 ± 23.0; (75.5) | 0.17 |
| | Life orientation | 54.2 ± 28.0; (54.2) | 56.4 ± 26.6; (58.3) | 0.64 |
| | Total score | 62.4 ± 19.8; (65.3) | 65.3 ± 17.4; (68.2) | 0.43 |

SD standard deviation, * HBsAg positive excluded, grey underlet are the more impaired values
# p value according to Mann-Whitney rank-sum test

*Table 2.* Quality of Life in HIV Positive Patients Determined by EQ-5D and HIV-SELT in Relation to anti-HCV (A) or HCV-RNA status* (B).

| **A** | | Anti-HCV +, n = 35 mean ± SD (median) IQR | Anti-HCV -, n = 154 mean ± SD (median) IQR | p value # |
|---|---|---|---|---|
| EQ-5D | Visual Analogue Scale (VAS) | 58.3 ± 22.2 (55.0) [40.0-80.0] | 71.0 ± 19.6 (75.0) [65.0 – 85] | 0.002; 0.016; 0.025 |
| HIV-SELT | Actual mood | 59.1 ± 24.7 (62.5) [45.0-76.9] | 73.9 ± 22.9 (81.3) [61.7-91.7] | 0.001; 0.001; 0.024 |
| | Physical impairments | 57.6 ± 21.9 (58.3) [41.7-79.2] | 65.0 ± 21.1 (66.6) [50.0-79.4] | 0.08; 0.68; 0.084 |
| | Subjective feeling | 48.6 ± 26.4 (50.0) [33.3-66.7] | 59.7 ± 26.2 (75.0) [41.7-83.3] | 0.023; 0.5; 0.017 |
| | Basic mood | 53.5 ± 24.5 (58.3) [33.3-75.0] | 67.9 ± 22.4 (75.0) [57.5-83.3] | 0.001, 0.002; 0.033 |
| | Social support | 60.0 ± 25.7 (62.5) [50.0-81.3] | 73.1 ± 21.0 (75.0) [61.5-88.5] | 0.005, 0.25; 0.004 |
| | Life orientation | 42.5 ± 26.7 (41.7) [25.-58.3] | 58.7 ± 25.8 (62.5) [40.6-75.0] | 0.001; 0.006; 0.017 |
| | Total score | 53.5 ± 19.1 (54.6) [37.2-68.8] | 66.4 ± 17.4 (70.3) [55.6-78.5] | 0.000; 0.01; 0.03 |
| **B** | | HCV-RNA +,n = 23 mean ± SD | HCV-RNA -, n = 10, mean ± SD | p value # |
| EQ-5D | Visual Analogue Scale (VAS) | 59.3 ± 23.3 | 55.3 ± 20.3 | 0.69 |
| HIV-SELT | Actual mood | 63.2 ± 25.4 | 48.7 ± 23.8 | 0.11 |
| | Physical impairments | 54.9 ± 22.0 | 60.8 ± 20.8 | 0.52 |
| | Subjective feeling | 45.3 ± 24.5 | 54.17 ± 32.0 | 0.52 |
| | Basic mood | 58.7 ± 23.6 | 44.2 ± 20.6 | 0.10 |
| | Social support | 58.1 ± 24.8 | 66.9 ± 23.0 | 0.38 |
| | Life orientation | 46.4 ± 26.5 | 36.3 ± 25.9 | 0.38 |
| | Total score | 54.5 ± 19.9 | 51.8 ± 18.7 | 0.77 |

Grey underlet are the more impaired values
# p value according to Mann-Whitney rank-sum test; 1. anti-HCV+ vs. anti-HCV-; 2. anti-HCV+ but HCV-RNA"-" vs. anti-HCV-; 3. anti-HCV+ & HCV-RNA"+" vs. anti-HCV-; * HCV-RNA status was only compared in anti-HCV positives

nificantly impaired quality of life in comparison to 154 anti-HCV negative patients in all categories (Table 2a). Interestingly, presence or absence of HCV-viraemia, determined by HCV-RNA by PCR, did not play any significant role (Table 2B), and actually the difference between anti-HCV positives but RNA negatives versus the anti-HCV negatives and between the anti-HCV & HCV-RNA positives versus the anti-HCV negatives was still significant (Table 2A). That's way this work is so important in our view, as more work in this direction is needed.

Actually, there was even a trend for HCV-RNA positive patients to be less impaired in emotional roles as indicated by lower impairment in "basic mood" and "actual mood" as well as "life orientation" (Table 2B)

As anti-HCV positive patients were more frequently unemployed this was included into a multiple regression analysis revealing two independent variables to be related to QoL. Showing that anti-HCV status ($p = 0.001$) was highly relevant, but slightly less relevant than employment ($p<0.001$), still both parameters being highly relevant concerning the HIV-Selt score. Similar results were obtained for the EQ-5D with $p<0.001$ for employment and $p = 0.011$ for anti-HCV.

As we previously reported that GBV-C is associated with better QoL we also included GBV-C status (22

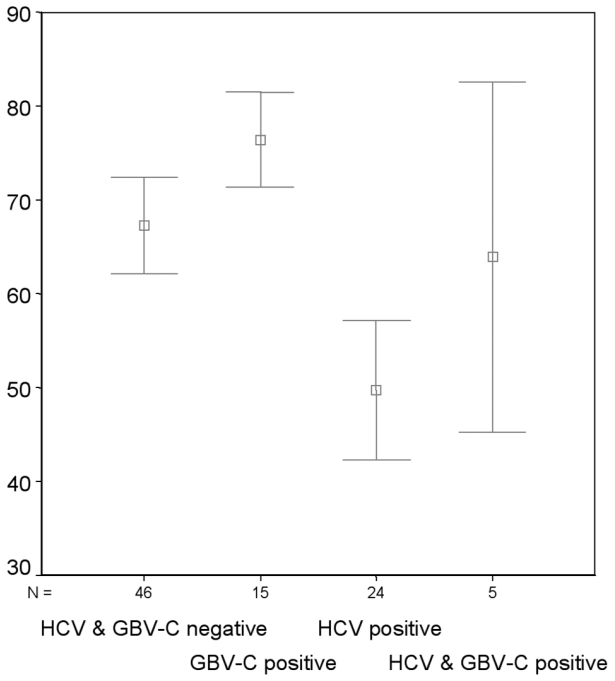


*Fig. 1.* Mean Score for HIV-SELT according to being negative or positive for either anti-HCV or GBV-C or both.

being viraemic and 76 being GBV-C non-viraemic) into this model, now revealing anti-HCV ($p<0.001$) being the most relevant factor followed by employment ($p = 0.02$), HIV viral load ($p = 0.029$) and GBV-C vireamia ($p = 0.042$) for HIV-SELT. Thus confirming both the importance of GBV-C for better QoL and the importance of HCV for worse QoL in HIV positive patients, which becomes obvious if QoL is analysed according to both GBV-C-RNA & anti-HCV status (see Fig. 1). The order of relevance was different for EQ-5D, with GBV-C being the most important ($p = 0.002$) followed by both employment (0.036) and anti-HCV status ($p = 0.042$).

Age, CD4 cell count, anti-HBc, anti-HCV, HBsAg status, HIV-viral load, CD4 cell count, CDC stage of HIV disease, and durations since diagnosis were all not significantly associated with impaired QoL.

## Discussion

It is of interest to note that the two hepatitis viruses HBV and HCV display a differential influence on the QoL in HIV-positive patients. While HBV does not impair QoL, it shows a significant impairment on survival.10 HCV does probably only moderately impair overall survival,10 but severely affects QoL as shown in this and other studies on HCV's association with QoL in HIV positive patients [17]. In addition, we believe it cannot be excluded that HCV-infection, which impairs the ability to concentrate [18, 19], may even be causal for the lower employment rate among HCV-positive individuals. Anyhow, the finding of severe impaired QoL in relation to HCV but not HBV is well in agreement with the recently observed low frequency (less than 5%) of depression during pegylated interferon therapy for HBV [20] while depression is seen in about 30% of HCV infected patients on pegylated interferon therapy [21, 22]. Thus our finding of the different effect of HBV and HCV on QoL in HIV-positive individuals is in accordance with the observation with non-HIV infected individuals.

Importantly, in our study there was no significant evidence that past HCV infection is associated with better QoL compared to ongoing HCV-infection. This is in contrast to most studies in non-HIV infected populations where it has been reported that patients clearing HCV due to interferon therapy have improved QoL [23, 24, 25]. HCV therapy was not widely used at the time of this study, as results usually were poor. HCV therapy is anyhow indicated only in case of liver disease and compliance, which usually lead to a dropout of more than 90% of the patients. Our results are supported by reports of "anti-D prophylaxis" infected woman [26], who cleared their HCV infection spontaneously or due to interferon therapy. Despite HCV clearance disabling impairment of QoL persisted. Our data are also in agreement with a study evaluating 93 anti-HCV positive women who showed impaired well-being compared to healthy controls but with no difference according to HCV-RNA status [27]. In addition, recent studies applying MRT-Spect to patients with presumed HCV-associated impairment of their well being, showed disturbances in the dopamine and serotonine system [28].

More research is required to understand the mechanism of how HCV infection leads to such significant impairment in patient well being irrespective of HCV clearance.

The retrospective approach used in this study has one potential advantage over future prospective studies. These questionnaires had been answered before the beneficial influence of GBV-C had been widely published in the medical [3, 4, 5] and the lay press, i.e. International Herald Tribune, and before more attention had been brought to impaired QoL in HCV infected patients. Thus, we can almost exclude that the knowledge of the GBV-C and hepatitis virus status and its correlation with QoL influenced the study outcome. This appears important, as knowledge of an infection associated with better or worse outcome might influence QoL [11].

As QoL was similarly impaired in HCV-viraemic and non-viraemic patients but better in GBV-C viraemic patients, this should be taken into account in case of planned interferon therapy, which might fail to clear HCV but clear the beneficial GBV-C.

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