HIV JournalView


David Wohl, M.D.

by David Alain Wohl, M.D.
University of North Carolina, AIDS Research and Treatment Unit

from The Body Pro

April 2004

View PDF

Table of Contents

GB Virus C -- Does It Affect HIV Progression? Two Longitudinal Studies, One Answer (Sort Of)

GB virus C (GBV-C, formerly known as hepatitis G) is a flavivirus closely related to the hepatitis C virus. Although GBV-C is fairly common in the general population, it has not been linked to clinical disease. The typical natural history of GBV-C infection in HIV-uninfected people is prolonged infection followed by spontaneous clearance. *In vitro* work has demonstrated that GBV-C replicates within CD4+ cells, and that once a lymphocyte is infected with HIV, coinfection with GBV-C reduces HIV replication within that cell.[1,2] Intriguing clinical data have suggested that coinfection with GBV-C and HIV delays HIV progression, leading to prolonged disease-free survival.[1,3-7] However, cross-sectional studies of HIV-infected cohorts have yielded inconsistent results, with a number of reports supporting[1,3-7] and others refuting[8-10] the effect GBV-C coinfection has on HIV progression.

In March, two longitudinal studies examining the impact of GBV-C on the natural history of HIV were published; reassuringly, these investigations arrive at overlapping and similar conclusions regarding the utility of GBV-C testing to predict the natural course of HIV infection in any individual.

However, the two research groups offer differing views on the significance of GBV-C infection in the setting of HIV. One team posits that coinfection may prove to be a model for novel HIV therapeutics and the other contends that detection of GBV-C may be a phenomenon related to HIV progression as opposed to an independent prognostic factor. Together, the studies highlight our current ignorance regarding the exact interaction between these viruses.

Persistent GB Virus C Infection and Survival in HIV-Infected Men

Williams CF, Klinzman D, Yamashita TE, Xiang J, Polgreen PM, Rinaldo C, et al. Persistent GB virus C infection and survival in HIV-infected men. N Engl J Med. 2004 Mar 4;350(10):981-90.

This study, published in the New England Journal of Medicine, was conducted among participants of the Multicenter AIDS Cohort (MACS), a U.S. cohort that has proved to be a wellspring for insights into the epidemiology, pathogenesis and management of HIV infection. The study, which is on-going, has followed a cohort of over 5,600 men who have sex with men since the 1980s, collecting data semiannually.

To examine the impact of GBV-C on HIV progression, stored specimens from participants with a known date of HIV seroconversion (within a window of one year) were tested at their 12- to 18-month visit after HIV seroconversion for current or previous GBV-C infection. Current infection was defined as having detectable viremia using GBV-C RNA PCR. Evidence of prior infection required detection of GBV-C surface envelope glycoprotein antibody (E2) -- an antibody that, in HIV-uninfected individuals, heralds the clearance of GBV-C viremia.

Data were presented on 271 men who had the requisite clinical data. A subset of 138 of these men had specimens collected not only at the 12- to 18-month visit following HIV seroconversion, but also at a visit five to six years later, permitting longitudinal evaluation. Importantly, to avoid confounding due to potent HIV therapy, the analyses included only data collected prior to 1996, before HAART became widely available.

At the visit proximate to HIV seroconversion, 107 patients (39%) had active GBV-C infection (GBV-C viral load detected and E2 antibody negative) and 124 (46%) had E2 antibody alone, indicating prior infection. Two subjects had both GBV-C viremia and E2 antibody. Thus, overall, 85% of the participants had current or prior GBV-C infection.

A patient's survival could not be predicted by whether he had GBV-C viremia at baseline. Baseline evidence of previous infection with the virus also did not predict survival. However, GBV-C status five to six years after HIV seroconversion *was* a significant and strong predictor of survival. Men who had persistent GBV-C infection were less likely to die compared to men who never had GBV-C infection or who had cleared their infection.

The risk of death among men who had GBV-C viremia at the 12- to 18-month visit, but did not have it five to six years later, was 5.87 times that of men who remained viremic. The men who did not have detectable GBV-C viremia at either time point, nor any evidence of prior infection, had an associated risk of death of 2.57 times that of men who remained viremic. This was similar to the 2.40 increased risk of mortality of men who were found to have the E2 antibody but no detectable GBV-C viremia during the study. Ten to 11 years after HIV seroconversion, the survival rate of the men with persistent GBV-C viremia was 75% compared to 39% for those who were persistently aviremic and 16% for the 12 men who cleared their viremia.

As would be expected, the effect of GBV-C coinfection on survival was not independent of CD4+ cell count or HIV-RNA PCR. Persistence of GBV-C infection was associated with a slower rate of CD4+ cell decay (-26 cells/mm^3 per year) compared to that of men who were E2 seropositive/ persistently aviremic (-70 cells/mm^3 per year), or men clearing GBV-C viremia (-107 cells/mm^3 per year). Likewise, HIV viremia increased less in the persistently viremic group. The investigators sought other confounders, including the presence of other viral hepatitis pathogens (very low prevalence rates of 6% for hepatitis B and 5% for hepatitis C were found) and the prevalence of heterozygosity for polymorphism of the CC chemokine receptor 5 (prevalence rate = 8%). They found that none were associated with differences in mortality.

This study provides powerful support for the notion that GBV-C is protective against HIV disease progression. Previous studies[9-10] that have not found a link between GBV-C and survival with HIV infection only enrolled patients with high CD4+ cell counts and had limited follow up.

In this study, CD4+ cell counts taken at the 12- to 18-month visit following HIV seroconversion were high and, as with prior studies, a near-term benefit of coinfection was not seen. However, with prolonged follow up, the association was uncovered.

Among patients who cleared their GBV-C infection, and thus risk hastened HIV disease progression, it is uncertain what happens first: GBV-C clearance followed by accelerated CD4+ cell decline or vice versa. As there were only two evaluation time points examined in this study, this remains unanswered.

Exactly how GBV-C can mitigate HIV disease is also not understood. An accompanying editorial[11] in the New England Journal of Medicine by Roger Pomerantz and Giuseppe Nunnari nicely reviews putative mechanisms by which GBV-C might interact with HIV, including the potential role GBV-C

viral proteins may play in blocking HIV entry into target cells. Mimicking the effect of GBV-C on the HIV lifecycle was optimistically suggested as a potential source of new agents to combat HIV infection.

GB Virus C During the Natural Course of HIV-1 Infection: Viremia at Diagnosis Does Not Predict Mortality

Björkman P, Flamholc L, Nauclér A, Molnegren V, Wallmark E, Widell A. GB virus C during the natural course of HIV-1 infection: viremia at diagnosis does not predict mortality. AIDS. 2004 Apr 9;18(6):877-86.

In a similarly designed study from Sweden, 230 patients with stored sera within two years of their HIV diagnosis, but prior to antiretroviral therapy (ART) initiation, were evaluated for GBV-C status. At baseline, 62 (27%) had GBV-C viremia, 69 (30%) had E2 antibodies and 99 (43%) had no evidence of current or previous GBV-C infection. Overall, 57% of the subjects in this cohort had markers for GBV-C infection, compared to 85% in the MACS cohort.

GBV-C viremia was significantly less prevalent in patients who were diagnosed with AIDS at baseline compared to those without AIDS. And, after a median of 4.3 years of follow up, GBV-C status at baseline did not predict all-cause mortality (death resulting from any cause), HIV-related mortality or AIDS incidence.

Follow-up serum specimens obtained near the time of ART initiation, death, progression to AIDS or a CD4+ cell count decline of 50% were available for 163 patients. Of these 163 patients, there were 11 patients who were viremic at baseline, but at follow up had undetectable GBV-C RNA and did not experience E2 seroconversion (i.e., they no longer had viremia but did not seroconvert).

Compared to the patients who were E2 antibody negative but had either persistent absence or persistent presence of GBV-C or had acquisition of the virus, these 11 patients experienced significantly higher rates of progression to AIDS and higher mortality.

During the study, 14 of the 163 subjects cleared their GBV-C viremia (including the 11 described above who did not become E2 antibody positive) and, of these, only three subjects developed E2 antibodies. This is remarkably similar to the data reported by the MACS group in which three of the 12 men who cleared their viremia developed E2 antibodies.

Interestingly, an analysis in which subjects were separated into two groups based on baseline clinical HIV disease stage/CD4+ cell count found that GBV-C viremia *was* associated with improved survival in those patients who had more advanced disease and/or a CD4+ cell count less than 300 cells/mm^3.

The findings of the Swedish group and the MACS group do not differ significantly. Overall prevalence of GBV-C infection was lower in the European study, although the proportion of patients with GBV-C clearance and persistence were not widely disparate.

While the MACS research team looked at their data and concluded the glass is half full (i.e., GBV-C status is *not* predictive of HIV progression at baseline but it is five to six years after HIV diagnosis), Bjorkman and colleagues looked at the same glass and declared it is half empty (i.e., baseline testing is useless and GBV-C clearance may be a consequence of accelerated HIV replication).

The Swedish group, pondering the chicken and egg question of which happens first (i.e., GBV-C clearance or HIV progression), leans heavily toward the conclusion that GBV-C replication responds negatively to HIV replication rather than the other way around. Because GBV-C and HIV are likely attempting to replicate within the same cells (i.e., CD4+ cells), in cases of advanced HIV infection, in which HIV replication is increased, GBV-C replication would be suppressed -- a scenario which may account for the lack of E2 antibodies among patients who cleared GBV-C viremia. Additionally, an intact immune system, replete with CD4+ cells in which GBV-C can replicate, may be required to maintain GBV-C viremia; with HIV progression and CD4+ cell count depletion, the pool of cells in which GBV-C can reproduce diminishes.

Conclusion

Both studies concur that a single determination of GBV-C status early in HIV infection does *not*

predict the clinical course of HIV -- although, in advanced HIV disease, it might.

The two investigations also detect an interaction between these viruses over time but are unable to identify the direction of the interaction. However, both studies are hamstrung by their limited number of patients and their lack of serial specimens with which to examine the interaction between HIV and GBV-C. If the Swedes are wrong, and GBV-C viremia actually does inhibit HIV replication, the mechanics by which GBV-C interferes with the HIV lifecycle could potentially provide a model for therapeutic interventions designed to mimic the beneficial effects of GBV-C.

GBV-C coinfection is a fascinating aspect of the HIV epidemic. More in-depth analyses of longitudinal studies are required to tease apart what this virus is or is not doing. Meanwhile, thoughts of intentional GBV-C infection are premature and may prove to be foolish given how little we know about this virus and what exactly it does over time in the bodies of people infected with HIV.

Long-Term Efficacy Data and Metabolic Effects of Lopinavir/Ritonavir

Long-Term Safety and Durable Antiretroviral Activity of Lopinavir/Ritonavir in Treatment-Naive Patients

Hicks C, King MS, Gulick RM, White Jr AC, Eron Jr JJ, Kessler HA, et al. Long-term safety and durable antiretroviral activity of lopinavir/ritonavir in treatment-naive patients: 4 year follow-up study. AIDS. 2004 Mar 26;18(5):775-9.

Most antiretrovirals receive approval from the U.S. Food and Drug Administration after presentation of 24- to 48-week clinical trial data. However, the long-term efficacy and safety of the drugs are of extreme importance to clinicians and patients, who must balance the desire for rapid availability of effective HIV therapies with concerns regarding the durability and safety of the drugs beyond the first year.

Lopinavir/ritonavir (LPV/r, Kaletra) is a potent and popular protease inhibitor (PI) combination that is included as a first-line option for the treatment of HIV infection in the latest U.S. Public Health Service guidelines.[12] Follow-up data on participants enrolled in an early clinical trial of lopinavir/ritonavir are reported by Hicks and colleagues.

Originally, 100 treatment-naive subjects with viral loads above 5,000 copies/mL and varying CD4+ cell counts, were randomized to one of three doses of lopinavir/ritonavir along with the NRTIs stavudine (d4T, Zerit) and lamivudine (3TC, Epivir).

After a year, all subjects received lopinavir/ritonavir 400 mg/100 mg twice a day plus stavudine and lamivudine. The mean baseline HIV-RNA level and CD4+ cell count were 4.89 log10 copies and 338 cells/mm^3, respectively. By week 204, 28 patients had dropped out of the study due to adverse events (10), loss to follow up (9), non-adherence (4), relocation (3), substance abuse (1) and primary provider choice (1).

Treatment was found to be extremely durable. By week 204, an impressive 70% of the subjects had a viral load below 50 copies/mL using an intent-to-treat analysis (on-treatment analysis resulted in a 97% rate of viral suppression below this lower limit of detection).

During the study, 15 subjects had sub-optimal virologic responses (defined as a viral load above 400 copies/mL on two consecutive measures or viral rebound followed by discontinuation of lopinavir/ritonavir, or failure to achieve a viral load below 400 copies/mL) and eight of these subjects subsequently discontinued the study drug. Genotypic resistance data from 10 of these patients revealed no primary or active site mutations in the protease region, although three subjects did have the lamivudine resistance-associated M184V mutation. CD4+ cell count responses were robust, with an overall mean increase from 281 to 721 cells/mm^3. Response to therapy was similar across all strata of patients regardless of their baseline CD4+ cell counts.

Of the 10 subjects who experienced treatment-limiting adverse events, seven of the cases were reported to be at least possibly related to the study drug. One patient had a myocardial infarction following spinal surgery and died. Two subjects had asymptomatic elevations of liver transaminases and another subject experienced symptomatic hepatic steatosis. Diarrhea, arthralgia and hyperlipidemia were other causes for treatment cessation.

Adverse events which did not lead to treatment discontinuation included, diarrhea in 36% of the subjects, nausea in 16%, abdominal pain in 10% and vomiting in 6%. Elevation of non-fasting lipids beyond 300 mg/dL was observed in 22% of the subjects, while 11% were found to have a grade 3 or greater transaminase (AST or ALT) level (this toxicity was more common in those with hepatitis B or C coinfection). Lipid-lowering therapy was prescribed to 19% of the subjects during the study. Body shape was not systematically evaluated.

Conclusion

These results are impressive and demonstrate that lopinavir/ritonavir, despite its warts (twice-daily dosing frequency, six large pills a day, gastrointestinal and metabolic toxicities), can continue to be taken by a majority of the patients who are prescribed the drug with lasting beneficial effects with regards to HIV infection.

In an accompanying editorial,[13] David Katzenstein applauded the study results, although he cautioned that the gastrointestinal and metabolic effects of PI therapy present a challenge to even longer term management of HIV infection, which is a perfect segue to the next article.

The Metabolic Effects of Lopinavir/Ritonavir in HIV-Uninfected Men

Lee GA, Seneviratne T, Noor MA, Lo JC, Schwarz J-M, Aweeka FT, et al. The metabolic effects of lopinavir/ritonavir in HIV-negative men. AIDS. 2004 Mar 5;18(4):641-9.

While lopinavir/ritonavir is undoubtedly one of the most potent antiretrovirals currently available, as hinted at in the four-year study described above, the drug, even in the absence of stavudine co-administration, has untoward effects on lipids and, like its classmates, is accused of altering body shape.

To examine this further, Lee and colleagues put lopinavir/ritonavir through the same wringer they put indinavir (IDV, Crixivan) through a few years ago.[14] In that study, as in this investigation, they administered the drug at standard dose to HIV-uninfected men for four weeks and measured a variety of metabolic parameters. Indinavir was clearly demonstrated to cause glucose intolerance and insulin resistance among the volunteers and laid to rest debate about whether the diabetes seen with this drug was a direct or indirect effect of this PI.

Studying the metabolic impact of antiretrovirals in HIV-uninfected volunteers provides the advantage of being able to examine the effect of the drug itself on these parameters, divorced from any contributions made by other HIV medication, immune reconstitution or HIV itself. However, the disadvantage of this approach is that the effects of the medication in HIV-uninfected individuals may be quite different than those in HIV-infected patients.

Ten subjects -- all Caucasian, except for one Hispanic participant -- were enrolled. They underwent a number of metabolic evaluations, including fasting glucose, insulin, lipids, oral glucose tolerance, insulin sensitivity by euglycemic hyperinsulinemic clamp, body shape by DEXA (dual energy x-ray absorptiometer), CT scan of the abdomen and BIA (bioelectrical impedance analysis) before and after. They were all admitted to an inpatient research unit where their diets were standardized for five days. Baseline measurements were then obtained and the subjects were discharged along with medication fitted with electronic monitoring devices. The men were then permitted to resume their normal diet and activity. Subjects were monitored weekly and then re-admitted for five days prior to the last set of measurements.

All 10 subjects completed the study. After four weeks of lopinavir/ritonavir, fasting triglyceride levels almost doubled from 78 mg/dL to 144 mg/dL in these HIV-uninfected subjects. There were no significant changes in total cholesterol or cholesterol subsets other than VLDL (very-low-density lipoproteins), which rose by 33%. In contrast to what these investigators had found with indinavir, lopinavir/ritonavir did *not* have a major impact on glucose, insulin or insulin resistance. However, there was a small but significant effect of lopinavir/ritonavir on two-hour oral glucose tolerance, with one subject demonstrating impaired glucose tolerance. Body composition did not change during the month-long study.

Conclusion

This study demonstrates that -- at least in HIV-uninfected men -- different PIs behave differently with regard to causing metabolic disturbances. Lopinavir/ritonavir had a dramatic effect on

triglycerides, but this was relatively less than the effect 500 mg of ritonavir (RTV, Norvir) twice a day had in a similar study[15] the authors previously conducted.

Likewise, as opposed to earlier work demonstrating an effect of PIs on total cholesterol and LDL (low-density lipoproteins)-cholesterol,[15-17] no such effect was seen here. The distinction between the impact of lopinavir/ritonavir and indinavir on glucose and insulin parameters is also notable. This is not to say that lopinavir/ritonavir has no effect on glucose metabolism -- the oral glucose tolerance testing did reveal a small effect -- however, this was substantially less than that seen with indinavir.

This study provides insight into the metabolic effects of this popular PI combination divorced from the influence of other antiretrovirals. It also advances our understanding of the potential mechanism behind the metabolic disturbances accompanying antiretroviral therapy. The finding that lopinavir/ritonavir increases triglycerides and VLDL cholesterol supports the hypothesis that it is increased *production*, rather than decreased clearance, of triglycerides that is at the root of PI-associated hypertriglyceridemia.

In addition, the fact that LDL cholesterol did *not* increase -- a finding consistent with previous studies of other PIs in HIV-uninfected volunteers -- strongly indicates that the PI class of antiretrovirals has minimal direct effects on LDL cholesterol and that restoration of health following potent combination therapy may be responsible for increases of LDL in the setting of HIV.

Further, the differential effects of PIs on glucose metabolism suggest that these drugs act in distinct ways on targets related to glucose regulation and point away from glucose dysregulation as a cause of hypertriglyceridemia. The work of this group of investigators demonstrates that we cannot paint all PIs with the same brush.

Lipid Screening in HIV-Infected Patients Receiving PI Therapy: How Adherent Are Healthcare Providers?

Korthuis PT, Asch SM, Anaya HD, Morgenstern H, Goetz MB, Yano EM, et al. Lipid screening in HIV-infected veterans. JAIDS 2004 Mar 4;35(3):253-60.

As the studies of lopinavir/ritonavir above illustrate, lipid abnormalities are not uncommon during PI therapy in HIV-infected individuals. Treatment guidelines[12] recommend healthcare providers check fasting triglyceride and cholesterol levels at baseline and every three to four months after treatment initiation. The investigators evaluated the degree to which clinicians adhere to these recommendations in the Veterans Administration (VA) system when caring for persons with HIV infection. The investigators examined data collected from all VA hospitals that cared for at least one HIV-infected person and assessed lipid screening frequency among HIV-positive patients receiving at least six months of PI-based therapy during 1999 to 2001.

Clinicians performed lipid screening within six months of therapy initiation in only 59% of 4,065 veterans who were taking PIs. These results are far worse than the 89% rate of lipid screening among diabetic veterans the authors cite. Given that the VA system is typically more successful in performing disease prevention screening than clinicians outside the VA, it is likely most healthcare providers have even lower rates of lipid screening than was seen in this study.

The investigators examined several factors associated with lipid screening and, in their analyses, receiving care at an urban VA hospital, previous hyperlipidemia, intravenous drug use and having an unknown HIV risk factor were significantly associated with a reduced likelihood for lipid screening.

Conclusion

It's disturbing that, even in the prevention-minded VA system, lipid screening frequency was sub-optimal. Certainly, lipid screening is often relegated to the back burner while more pressing issues are dealt with. This may explain why, in more complicated patients, such as intravenous drug users, screening was less likely to occur. However, even among patients in the cohort with advancing age, diabetes and prior hyperlipidemia, screening rates did not exceed 71%.

The finding that rural hospitals were less likely to screen for lipid abnormalities than urban-based

centers is also troubling and points to disparities in care that need to be addressed. Provider and patient education and systemic interventions to improve quality of care -- especially in rural areas -- are methods that should be undertaken.

Heterosexual Transmission of HIV -- We Are Catching Up to the Rest of the World

Heterosexual transmission of HIV -- 29 states, 1999-2002. MMWR. 2004 Feb 20;53(6):125-9.

You would not know it by asking your average man or woman on the streets of Los Angeles, New York or, where I am, Chapel Hill, North Carolina, but the major mode of HIV transmission on planet Earth is sex between a man and a woman. Two decades into the HIV pandemic and heads remain in the sands of isolated ignorance. That is likely to change.

In the United States, only 29 states meet the U.S. Centers for Disease Control (CDC)'s standards for HIV reporting (three cheers for federalism) and are thus able to provide data on the incidence of HIV, rather than just new diagnoses of AIDS.

An analysis of the HIV infection rates in persons over 12 years of age in these states was conducted by the CDC. During 1999-2002, an astounding 101,877 cases of HIV infection were diagnosed in these 29 states. Of these, 36,084 (35%) were reported to be heterosexually acquired. Almost two thirds (64%) of the cases of heterosexual HIV transmission occurred in women and 74% occurred in non-Hispanic blacks. Together with Hispanics, non-Hispanic blacks accounted for 84% of heterosexually acquired HIV -- although these groups only constituted 21% of the population of the 29 states. Among those aged 13-19 with heterosexually acquired HIV infection, 89% were female.

Conclusion

These are clearly alarming and disturbing data. Over 100,000 people were infected with HIV in this country during the few years included in this report -- this despite millions of dollars spent on prevention efforts. Further, the report highlights how the epidemic in the United States is shifting. Heterosexual transmission of HIV is increasing and the virus is finding a niche in populations that are generally more impoverished, are likely to have less access to care and are arguably not at the receiving end of the HIV prevention messages emanating from the CDC's headquarters in Atlanta. The sexually transmitted disease/HIV prevention community has learned what does not work and over the past few years has shifted efforts from a "buyer beware" approach typified by getting HIV-uninfected people to embrace condoms, to a model more appropriate to containing contagion, specifically, identifying infected individuals and via treatment and/or counseling render them less infectious to others.

According to the CDC, perhaps a quarter of the 900,000-1,000,000 people living with HIV in this country do not know they are HIV-infected.[18] This important report points us in the direction we need to head if we are to increase the opportunities for diagnosing persons with HIV infection and preventing their role in the promulgation of the epidemic.

Certainly, the key to preventing HIV is the screening of sexually active heterosexual men and women. Each of us who cares for persons living with HIV needs to not only ponder which antiretroviral would be best for a particular patient but should also wonder whether that patient practices safe sex.

Think about the last 10 patients with HIV you have seen and ask yourself whether for each of them you know (*really know*) the answer to that last question. If you don't, you need to. The extra precious time you spend discussing safe sex and drug use may just prevent one case of HIV -- and that is one less case for inclusion in the CDC's next issue of the Morbidity and Mortality Weekly Report.

Please fill out this quick survey and tell us what you think of this HIV JournalView article!

References

1. Xiang J, Wünschmann S, Diekema DJ, Klinzman D, Patrick KD, George SL, et al. Effect of coinfection with GB virus C on survival among patients with HIV infection. N Engl J Med.

2001 Sep 6;345(10):707-14.

2. Xiang J, Wünschmann S, Schmidt W, Shao J, Stapleton JT. Full-length GB virus C (hepatitis G virus) RNA transcripts are infectious in primary CD4-positive T cells. J Virol. 2000 Oct;74 (19):9125-33.

3. Heringlake S, Ockenga J, Tillmann HL, Trautwein C, Meissner D, Stoll M, et al. GB virus C/ hepatitis G virus infection: a favorable prognostic factor in human immunodeficiency virus-infected patients? J Infect Dis. 1998 Jun;177(6):1723-6.

4. Toyoda H, Fukuda Y, Hayakawa T, Takamatsu J, Saito H. Effect of GB virus C/hepatitis G virus coinfection on the course of HIV infection in hemophilia patients in Japan. J Acquir Immune Defic Syndr Hum Retrovirol. 1998 Mar 1;17(3):209-13.

5. Lefrère J-J, Roudot-Thoraval F, Morand-Joubert L, Petit J-C, Lerable J, Thauvin M, et al. Carriage of GB virus C/hepatitis G virus RNA is associated with a slower immunologic, virologic, and clinical progression of human immunodeficiency virus disease in coinfected persons. J Infect Dis. 1999 Apr; 179(4):783-9.

6. Yeo AET, Matsumoto A, Hisada M, Shih JW, Alter HJ, Goedert JJ. Effect of hepatitis G virus infection on progression of HIV infection in patients with hemophilia [brief communication]. Ann Intern Med. 2000 Jun 20;132(12):959-63.

7. Tillmann HL, Heiken H, Knapik-Botor A, Heringlake S, Ockenga J, Wilber JC, et al. Infection with GB virus C and reduced mortality among HIV-infected patients. N Engl J Med. 2001 Sep 6;345(10):715-24.

8. Sabin CA, Devereux H, Kinson Z, Griffioen A, Brown D, Dusheiko G, et al. Effect of coinfection with hepatitis G virus on HIV disease progression in hemophilic men [letter]. J Acquir Immun Defic Syndr Hum Retrovirol. 1998 Dec 15;19(5):546-8.

9. Birk M, Lindbäck S, Lidman C. No influence of GB virus C replication on the prognosis in a cohort of HIV-1-infected patients. AIDS. 2002 Dec 6;16(18):2482-5.

10. Brust D, Jagannatha S, Herpin B, Miller K, Metcalf J, Lau D, et al. Hepatitis G virus (HGV) infection does not prolong survival of patients with early-stage HIV disease: importance of baseline HIV viral load as a predictor of mortality. Presented at: XIV International AIDS Conference; 2002 Jul 7-12; Barcelona, Spain. Abstract WeOrC1378.

11. Pomerantz RJ, Nunnari G. HIV and GB virus C -- can two viruses be better than one? N Engl J Med. 2004 Mar 4;350(10):963-5.

12. Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2004 Mar 23.

13. Katzenstein D. The longer the better? four years of durable, initially boosted protease treatment. AIDS. 2004 Mar 26;18(5):811-3.

14. Noor MA, Lo JC, Mulligan K, Schwarz J-M, Halvorsen RA, Schambelan M, et al. Metabolic effects of indinavir in healthy HIV-seronegative men. AIDS. 2001 May 4;15(7):F11-F18.

15. Purnell JQ, Zambon A, Knopp RH, Pizzuti DJ, Achari R, Leonard JM, et al. Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. AIDS. 2000 Jan 7;14(1):51-7.

16. Segerer S, Bogner JR, Walli R, Loch O, Goebel FD. Hyperlipidemia under treatment with proteinase inhibitors. Infection. 1999 Mar-Apr;27(2):77-81.

17. Berthold HK, Parhofer KG, Ritter MM, Addo M, Wasmuth JC, Schliefer K, et al. Influence of protease inhibitor therapy on lipoprotein metabolism. J Intern Med. 1999 Dec;246(6):567-75.

18. Fleming PL, Byers RH, Sweeney PA, Daniels D, Karon JM, Janssen RS. HIV prevalence in the United States, 2000. Presented at: 9th Conference on Retroviruses and Opportunistic Infections; 2002 Feb 24-28; Seattle, Wash. Abstract 11.

For a complete index of The Body Pro's HIV JournalViews, click here.

Please note: Knowledge about HIV changes rapidly. Note the date of this article, and before treating patients or employing any therapies described in these materials, verify all information independently. If you are a patient, please consult a doctor or other medical professional before acting on any of the information presented in this article.