GBV-C is considered as a prognostic or therapeutic tool for the care of patients with HIV infection.

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1. Canducci F, Uberti Foppa C, Boeri E, et al. Characterization of GBV-C infection in HIV-1 infected patients. J Biol Regul Homeost Agents 2003;17:191-4.

**THE AUTHORS REPLY:** Does GBV-C prolong survival in HIV-positive persons, or is it a marker of high CD4+ cell counts? In our study, men with HIV seroconversion who had persistent GBV-C viremia were 2.4 times as likely to survive as were persons who did not have viremia at either time point (95 percent confidence interval, 1.2 to 5.2; $P<0.01$), strongly supporting a causal role for GBV-C. The duration of HIV infection in men with and without GBV-C was the same, and the stage of HIV disease was not based on surrogate markers. Nevertheless, we found that the CD4+ cell count and the plasma HIV RNA concentration were related to GBV-C status. We also demonstrated prolonged survival in HIV-positive men with baseline CD4+ cell counts of less than 50 per cubic millimeter.[1] The relative protection conferred by persistent GBV-C viremia in men with HIV seroconversion was greater than that observed for men who were heterozygous for the CC chemokine receptor 5 (CCR5) Δ32 polymorphism in the HIV coreceptor gene.[2] As mentioned in the Discussion section of our article, we agree that it is important to determine whether the decline in CD4+ cells occurs before the clearance of GBV-C or whether the loss of GBV-C is associated with more rapid CD4+ cell decline. Ongoing studies in persons with HIV seroconversion should answer this question.

We also agree that demonstration of viral interference or other mechanisms to explain this epidemiologic association is important. We have previously shown that in vitro coinfection of lymphocytes with GBV-C and HIV results in decreased HIV replication.[1] The HIV-inhibitory effect is mediated by the induction of beta-chemokines and the downregulation of the HIV coreceptor CCR5,[3] possibly as a result of interactions between GBV-C E2 protein and CD81.[4] Furthermore, clinical studies have demonstrated decreased CCR5 expression on CD4+ lymphocytes[4] and favorable type 1 and 2 helper-T-cell cytokine profiles among GBV-C–HIV coinfected people, as compared with those without GBV-C viremia.[5] The combination of eight epidemiologic studies demonstrating a survival benefit in GBV-C–infected HIV-positive people, combined with growing evidence of interference between these two viruses, strongly suggests that in HIV-infected people there is a causal relationship between GBV-C and prolonged survival.

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## Drug-Induced Prolongation of the QT Interval

**TO THE EDITOR:** Roden (March 4 issue)[1] provides a concise review of drug-induced prolongation of the QT interval. However, in Table 2 of the article, which lists risk factors for torsade de pointes, diet and fasting are not mentioned. There have been several reports of prolongation of the QT interval and associated torsade de pointes resulting from protein-sparing diets, starvation, anorexia nervosa, and fasting during a hunger strike.[2-5] Consequently, physicians should pay particular attention whenever prescribing QT-interval–prolonging drugs in patients in such circumstances.

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**TO THE EDITOR:** New data could be added to Roden's review. First, only 19 percent of QT-related arrhythmias due to the use of noncardiac drugs strike within 72 hours after the initiation of therapy.[1] Thus, starting noncardiac drugs that have the potential for causing prolongation of the QT interval while the patient is under observation (as recommended for antiarrhythmic drugs)[2] would be futile in most cases. Second, 96 percent of patients in whom torsade de pointes develops in association with the use of noncardiac drugs have at least one risk factor, and 72 percent have two risk factors, that can be easily identified before administration of the culprit drug is initiated. These risk factors include female sex; cardiac, renal, or liver disease; hypokalemia; a history of the long-QT syndrome; and prescription of a QT-prolonging medication in excessive doses or in combination with a second drug that impairs its metabolism or further prolongs the QT interval.[1] Finally, only "arrhythmia specialists" can reliably recognize a long QT interval. Other physicians, including many cardiologists, are likely to miss a prolonged QT.[3] Accordingly, strategies could be developed for the physician prescribing medication with the potential for causing prolongation of the QT interval.[3]

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**TO THE EDITOR:** Clinical measurement of the QT interval is subject to substantial variability, which can cloud interpretation, owing to factors such as circadian effects, differences in autonomic tone, electrolytes, and intraobserver and interobserver variability.[1,2] Obviously, there are unavoidable limitations, but methodologic improvements should be feasible. In February 2002, the Food and Drug Administration International Conference on Harmonization S7B guidelines were proposed; they provide more specific direction for the testing of new drugs for cardiac safety.[3]

Nevertheless, no data exist about how and when to monitor the QT interval during pharmacotherapy. As medical oncologists involved in phase 1 studies, we find assessment of the corrected QT interval (QTc) before and during drug administration a key way to enhance risk management of QT-interval–prolonging medications. Specific guidance is needed in order to standardize cardiovascular testing of anticancer and other drugs with potential health benefits. Guidelines should consider each patient's pharmacogenomic profile, the pharmacokinetics of drugs, and the time of administration in order to determine the timing of QTc assessment.

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**TO THE EDITOR:** In his review of QTc prolongation, Roden cites www.torsades.org,[1] the Web site of the Arizona Center for Education and Research on Therapeutics (CERT), as the primary reference for drugs associated with this effect. To assess the validity of this source, we compared the risk levels assigned to drugs on this Web site with those published by Al-Khatib et al.[2] Generic names from both lists were compared between the two data sets. Table 1 shows a cross-tabulation of risk levels from the two sources. Forty-nine drugs are listed only by the Arizona CERT, and six are listed only in the article by Al-Khatib et al. Comparing levels of risk for the 34 drugs that are listed in both sources and that are

**Table 1. Comparison of Risks of Prolongation of the Corrected QT Interval Associated with Drugs Listed in Two Sources.***

| Risk Levels According to Arizona CERT | Risk Levels According to Al-Khatib et Al. | | | | | | |
|---|---|---|---|---|---|---|---|
| | QTcP Very Probable | QTcP Probable | QTcP Possible in High-Risk Patients | QTcP Improbable | QTcP Very Improbable | Risk Unknown | Not Listed |
| | *number of drugs* | | | | | | |
| Generally accepted as a risk factor for TdP | 8 | 1 | 7 | 1 | 0 | 3 | 5 |
| May be associated with TdP | 0 | 1 | 3 | 1 | 3 | 10 | 13 |
| Should be avoided in patients with congenital long-QT syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 21 |
| Unlikely risk factor | 0 | 0 | 4 | 4 | 1 | 1 | 10 |
| Not listed | 0 | 0 | 1 | 2 | 1 | 2 | — |

* The sources compared are the Web site of the Arizona Center for Education and Research on Therapeutics (CERT)[1] and an article by Al-Khatib et al.[2] QTcP denotes prolongation of the corrected QT interval, and TdP torsade de pointes.

not listed as having "unknown" risk by Al-Khatib et al. results in a Kendall's tau nonparametric correlation[3] of 0.51, which is significant (P=0.001) but indicates a poor level of agreement. Despite extensive research on risk factors for QTc prolongation,[4] there is still substantial discrepancy among experts about the drugs that may cause this complication.

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**DR. RODEN REPLIES:** I concur with Viskin and colleagues' contention that detailed screening — beyond the assessment of demographic factors — is unlikely to be useful in the prevention of marked QT-interval prolongation and associated arrhythmias due to "noncardiac" drugs.

Curigliano et al. reiterate the difficulty of accurately measuring small changes in the QT interval and emphasize the need to incorporate pharmacokinetic considerations into standardized cardiovascular testing of noncardiac drugs. They also argue for consideration of each patient's pharmacogenomic profile. Although I look forward to the day when genomic information is routinely incorporated into clinical decision making and drug development, the technology required for implementation of this vision is still immature. Meanwhile, I urge investigators and companies involved in drug development to obtain, with appropriate consent, DNA samples from patients participating in clinical trials — a valuable resource for pharmacogenetic research.

Korantzopoulos and Siogas point out that extreme fasting and associated conditions are risk factors for prolongation of the QT interval and sudden death. I agree that in these extreme conditions any drug therapy should be used judiciously and very close attention be paid to maintenance of normal electrolyte levels.

Cruciani and colleagues point out discrepancies between the lists presented on www.torsades.org and those presented by Al-Khatib et al. Both lists were generated by polling experts, an imperfect approach that reinforces the small numerators and very large denominators at hand when one is studying rare drug-related adverse effects. In fact, I am struck by the concordance between the two lists, and I note that the disagreements do not occur in the extreme categories ("very probable" or "improbable"). I believe the two lists reflect a reasonable summary of culprit drugs as we now understand them. As I discuss in my review, it is not so clear how to classify newer drugs associated with

small or moderate QT-interval prolongations but no torsade de pointes or drugs in very widespread use with a few verifiable cases of torsade de pointes. Nevertheless, the recent history of drug-induced QT-interval prolongation reinforces the concept that physicians must remain alert to the possibility that arrhythmias or other unexpected clinical outcomes may be related to drugs.

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## EBV and Burkitt's Lymphoma

**TO THE EDITOR:** In their review of the persistence of the Epstein–Barr virus (EBV) and the origins of associated lymphomas (March 25 issue),[1] Thorley-Lawson and Gross state, "There is no satisfactory explanation of how EBV participates in the pathogenesis of Burkitt's lymphoma." However, recently, Niller and colleagues proposed a new model for the development of Burkitt's lymphoma.[2] In their model, a central role is played by the EBV-encoded RNA (EBER) locus of the EBV genome, the product of which has been implicated in EBV-related tumorigenesis, mainly by inhibiting apoptosis.[3] The authors based their hypothesis on a binding site for c-Myc in the promoter region of EBER. They proposed that in an EBV-infected B cell (a type I latency cell expressing EBV nuclear antigen 1 and EBER) undergoing the germinal-center reaction, a translocated and deregulated c-Myc directly up-regulates the antiapoptotic EBER-transcription units.[4] In this way, the balance between apoptosis and antiapoptosis (sustained by c-Myc and EBER, respectively) would be permanently shifted in favor of cell survival, allowing c-Myc to express its oncogenic potential and drive lymphomagenesis in the EBV-infected cell.[5]

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**DR. THORLEY-LAWSON REPLIES:** Rossi and Bonetti offer an interesting explanation of the role of EBV in the pathogenesis of Burkitt's lymphoma. However, what they describe is one scenario among several, all of which lack compelling evidence. This further illustrates our point that no satisfactory explanation of the involvement of EBV in Burkitt's lymphoma has been presented for which there is convincing evidence that is broadly accepted by the scientific community. In comparison, c-Myc is a risk factor for Burkitt's lymphoma that meets this standard. It is widely accepted to have a role in Burkitt's lymphoma, because it is known to regulate cell growth and apoptosis[1] and is always translocated and deregulated in Burkitt's lymphoma.[2,3] Furthermore, there is ample evidence (e.g., from mouse transgenics) that deregulated c-Myc contributes directly to the development of B-cell lymphomas, including Burkitt's lymphoma.[4,5] Unlike c-Myc, all models of EBV involvement in Burkitt's lymphoma to date lack such overwhelming evidence. The scenario of Rossi and Bonetti may one day achieve the credibility of a satisfactory explanation, but we would not bet the house on it.

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