MAJOR ARTICLE

Gilbert Syndrome and the Development of Antiretroviral Therapy–Associated Hyperbilirubinemia

Margalida Rotger,[1] Patrick Taffé,[2] Gabriela Bleiber,[1] Huldrych F. Günthard,[3] Hansjakob Furrer,[4] Pietro Vernazza,[5] Henning Drechsler,[6] Enos Bernasconi,[7] Martin Rickenbach,[2] Amalio Telenti,[a] and the Swiss HIV Cohort Study

[1]Institute of Microbiology and Service of Infectious Diseases, University of Lausanne, and [2]Swiss HIV Cohort Study Data Center, Lausanne, [3]Division of Infectious Diseases and Hospital Epidemiology, University Hospital, Zurich, [4]Division of Infectious Diseases, University Hospital, Bern, [5]Division of Infectious Diseases, Kantonsspital, St. Gallen, [6]Division of Infectious Diseases, University Hospital, Basel, and [7]Division of Infectious Diseases, Ospedale Regionale di Lugano, Lugano, Switzerland

Background. Unconjugated hyperbilirubinemia results from Gilbert syndrome and from antiretroviral therapy (ART) containing protease inhibitors. An understanding of the interaction between genetic predisposition and ART may help to identify individuals at highest risk for developing jaundice.

Methods. We quantified the contribution of *UGT1A1*28* and ART to hyperbilirubinemia by longitudinally modeling 1386 total bilirubin levels in 96 human immunodeficiency virus (HIV)–infected individuals during a median of 6 years.

Results. The estimated average bilirubin level was 8.8 μmol/L (0.51 mg/dL). Atazanavir increased bilirubin levels by 15 μmol/L (0.87 mg/dL), and indinavir increased bilirubin levels by 8 μmol/L (0.46 mg/dL). Ritonavir, lopinavir, saquinavir, and nelfinavir had no or minimal effect on bilirubin levels. Homozygous *UGT1A1*28* increased bilirubin levels by 5.2 μmol/L (0.3 mg/dL). As a consequence, 67% of individuals homozygous for *UGT1A1*28* and receiving atazanavir or indinavir had ⩾2 episodes of hyperbilirubinemia in the jaundice range (>43 μmol/L [>2.5 mg/dL]), versus 7% of those with the common allele and not receiving either of those protease inhibitors ($P < .001$). Efavirenz resulted in decreased bilirubin levels, which is consistent with the induction of UDP-glucuronosyltransferase 1A1.

Conclusions. Genotyping for *UGT1A1*28* before initiation of ART would identify HIV-infected individuals at risk for hyperbilirubinemia and decrease episodes of jaundice.

Unconjugated bilirubin needs to be conjugated with glucuronic acid to be excreted in the bile. This step is mediated by the microsomal enzyme UDP-glucuronosyltransferase (UGT). Fifteen UGT isoforms with different substrate specificities, including the bilirubin-specific isoform UGT1A1, have been identified [1]. Reduced activity of this enzyme leads to unconjugated hyperbilirubinemia.

Gilbert syndrome is the most common inherited cause of unconjugated hyperbilirubinemia, and it occurs in 3%–10% of the general population [2]. The influence of a polymorphism in the promoter TATA element of the gene encoding UGT1A1 has been extensively investigated in the context of Gilbert syndrome. Promoters containing 7 thymine adenine (TA) nucleotide repeats, $A(TA)_7TAA$ (the *UGT1A1*28* allele), are less active than is the common promoter containing 6 TA repeats. Thus, homozygosis for the allele $A(TA)_7TAA$ leads to higher levels of unconjugated bilirubin [2–4]. The allelic frequency of this polymorphism differs among racial groups. It is more common in African Americans ($f = 0.43$), whites ($f = 0.36$–0.39), and Indians ($f = 0.35$) and less common in Japanese ($f = 0.11$), Chinese ($f = 0.16$), and Malaysians ($f = 0.19$) [3, 5–7]. In addition to the *UGT1A1*28* allele, other polymorphisms in the *UGT1A1* gene have been

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[a] The study team members are listed after the text.

Reprints or correspondence: Dr. Amalio Telenti, Institute of Microbiology, University of Lausanne, 1011 Lausanne, Switzerland (amalio.telenti@hospvd.ch).

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associated with Gilbert syndrome in the Japanese population [8–10].

Unconjugated hyperbilirubinemia is also a recognized adverse effect of protease inhibitor (PI) therapy containing indinavir (IDV) or atazanavir (ATV) [11–13]. The pathophysiological bases of this adverse effect may be the same as those in Gilbert syndrome. Zucker et al. reported that IDV induces hyperbilirubinemia by competitive inhibition of the UGT1A1 enzyme and found a strong association between the homozygous variant allele $A(TA)_7TAA$ and the risk of developing hyperbilirubinemia while receiving IDV [14].

In the present study, we used a longitudinal approach to model the influence that the *UGT1A1*28* allele has on antiretroviral therapy (ART)–associated hyperbilirubinemia. The aim of the study was to (1) quantify the degree of elevation in bilirubin levels in association with various PIs, (2) assess the interaction between the presence of the *UGT1A1*28* allele and the ART regimen, and (3) identify individuals at risk of developing jaundice after the initiation of ART.

PARTICIPANTS, MATERIALS, AND METHODS

Study participants. A total of 96 participants were recruited from the genetics project of the Swiss HIV Cohort Study (information available at: http://www.shcs.ch). The ethics committees of all participating centers approved the genetics project, and all participants gave written, informed consent for genetic testing. The study population was a convenience sample as determined by a preliminary analysis of the allelic frequency and the size of the genetic effect. The selection criteria included having received ATV, IDV, or lopinavir (LPV) at at least 1 time point during follow-up. The study period was defined as the follow-up period starting with the first study visit at which bilirubin levels were measured (beginning in 1994) until November 2004. Total bilirubin and conjugated bilirubin levels were measured. The unconjugated bilirubin level was calculated by subtracting the conjugated bilirubin level from the total bilirubin level. Hyperbilirubinemia was graded in accordance with the AIDS Clinical Trials Group guidelines for total bilirubin levels: grade 1 (mild), 23–32 μmol/L (1.3–1.9 mg/dL); grade 2 (moderate), 33–53 μmol/L (1.9–3.1 mg/dL); grade 3 (severe), 54–105 μmol/L (3.1–6.1 mg/dL); and grade 4 (serious), >105 μmol/L (>6.1 mg/dL) [15]. Jaundice was defined as a total bilirubin level >43 μmol/L (>2.5 mg/dL) [16].

Genetic analyses. Genomic DNA was extracted from frozen peripheral blood mononuclear cells. Genotyping was performed by direct sequencing by use of forward (5′-AAGTGAACTCCCTGCTACCTT-3′) and reverse (5′-CCACTGGGATCAACAGTATCT-3′) primers, described elsewhere [5], to generate a product that was 253–255 bp.

Statistical analysis. The data were analyzed longitudinally by modeling the individual effects of the different covariables on log-transformed total bilirubin levels. We used the log transformation instead of the linear scale, to stabilize variances and obtain a more symmetric distribution. The analysis used a multivariate model proposed by Diggle [17, 18] in which the covariance structure arises from the consideration of 3 residual components. This approach allows for disentanglement of the total variation into 3 distinct dimensions: (1) a random effect accounting for the propensity of individuals with intrinsically high or low bilirubin levels, (2) a stationary Gaussian process to allow for some correlation between the repeated measurements from the same individual, and (3) a residual error term. This approach is particularly relevant for cohort data, so that an economical and plausible covariance structure can be obtained. The specific advantages include the ability to accommodate unbalanced repeated measurements made at irregular time intervals—as is usually the case with cohort data—to generate a flexible correlation structure with few parameters to be estimated and thereby allowing more precise inferences, a straightforward interpretation of regression coefficients, and a better understanding of the sources of variability [19, 20]. Our model assumes that the covariances are stationary. However, an informal check of the assumed covariance structure as well as of the importance of each component can be gained by nonparametrically estimating the empirical semivariogram [18, 21].

Covariables included in the regression model were ART regimen, age, sex, hepatitis C and B serostatus, comedication (cotrimoxazole, pyrimethamine, or rifampin), smoking status, hemoglobin level, and the genetic factor tested. On the basis of an initial assessment of the impact that each individual antiretroviral drug had on the bilirubin level in an additive multivariate model, the ART agents were grouped as follows: (1) no ART at the time that bilirubin level was measured, (2) ART containing only nucleoside reverse-transcriptase inhibitors (NRTI ART), (3) ART containing NRTI and nonnucleoside reverse-transcriptase inhibitors (NNRTI ART), and ART containing PIs (PI ART), including (4) ATV, (5) IDV, (6) LPV, (7) nelfinavir (NFV), (8) saquinavir (SQV), and (9) full-dose ritonavir (RTV). For adjustment for confounding variables, cross-sectional and longitudinal relationships between the continuous explanatory variables and the response were distinguished [19, 22], and adequate functional form was assessed by use of fractional polynomials [23]. Goodness of fit was evaluated by comparing mean observed and predicted measurements, as well as residuals, on time plots of values in strata defined by polymorphisms and ART regimens. We also compared the estimated variogram from our multivariate model with the nonparametric estimate [17, 18, 21].

The analysis of interactions between genotypes and ART regimens was first tested globally. If the global test was significant, subcategories contributing to the *P* value were screened, and

Table 1. Characteristics of the study participants.

Characteristic	Study participants
Baseline age, median (IQR), years	38.3 (34.2– 46.2)
Men/women, no. (% men)	77/19 (80.2)
Ethnicity	
White	92 (95.8)
African	1 (1.0)
Hispanic	3 (3.1)
Presumed HIV transmission route	
Homosexual sex	43 (44.8)
Heterosexual sex	27 (28.1)
Injection drug use	23 (24.0)
Unknown	3 (3.1)
Duration of follow-up, median (IQR), years	6 (3.9–7.3)
Positive for hepatitis C antibodies	24 (25.0)
Positive for hepatitis B antigen	2 (2.1)

NOTE. Data are no. (%) of participants, unless otherwise indicated. IQR, interquartile range.

significant and consistent strata were retained. All statistical analyses were conducted using Stata (version 8.2 for Windows; StataCorp) and SAS (version 8.02; SAS Institute).

RESULTS

Study participants. The *UGT1A1*28* allele was present with an allelic frequency of 0.41 and followed Hardy-Weinberg equilibrium. The characteristics of the study participants and the median total bilirubin levels during the follow-up period are summarized in table 1. A total of 1386 total bilirubin and 226 unconjugated bilirubin levels were recorded during the study period. Analyses showed a highly significant correlation between the *UGT1A1* genotype and log-transformed total and unconjugated bilirubin levels ($r = 0.95$). These results allowed the elaboration of a longitudinal model using the log-transformed total bilirubin level as the phenotype. The key results were thereafter confirmed on the data set of unconjugated bilirubin levels (see below).

The median number of measurements of total bilirubin levels during the follow-up period was comparable in study participants with normal ($\leqslant$23 μmol/L [1.3 mg/dL]; $n = 10$ measurements) and elevated (>23 μmol/L [1.3 mg/dL]; $n = 15.5$ measurements) total bilirubin values. Of the covariables tested, hemoglobin levels and chronic hepatitis C or B infection were associated with increased bilirubin levels (table 2).

Effect of ART on bilirubin levels. A total of 152 total bilirubin levels (11%) were measured in the absence of ART; 57 (4.1%) were measured in participants who received NRTI ART; 49 (3.5%) were measured in participants who received NNRTI ART; and 1128 (81.4%) were measured in participants who received PI ART that contained ATV ($n = 185$; 13.3%), IDV ($n = 534$; 38.5%), LPV ($n = 152$; 11.0%), NFV ($n = 149$; 10.8%), RTV ($n = 32$; 2.3%), or SQV ($n = 76$; 5.5%). The median number of changes in the ART regimen per individual was 3 (range, 1–14 changes). The influence of ART on total bilirubin levels is shown in table 2. ATV had a stronger association with elevated total bilirubin levels than IDV did. We evaluated the effect of receiving ATV or IDV alone or in combination with RTV. We did not find significant differences ($P = .30$) in the estimated effect on total bilirubin levels for individuals who received ATV alone (0.38 $\log_{10}$ μmol/L), ATV in combination with RTV (0.45 $\log_{10}$ μmol/L), IDV alone (0.27 $\log_{10}$ μmol/L), or IDV in combination with RTV (0.31 $\log_{10}$ μmol/L). The estimated average bilirubin level was 8.8 μmol/L (0.51 mg/dL). PI ART containing ATV increased this level by an estimated 15 μmol/L (0.87 mg/dL), and PI ART containing IDV increased this level by 8 μmol/L (0.46 mg/dL). LPV, NFV RTV, and SQV had modest effects on total bilirubin levels. NNRTI ART (consisting of efavirenz in 98% of the data points) was associated with a decrease of 3.1 μmol/L (0.18 mg/dL) in total bilirubin levels.

Effect of the* UGT1A1*28 *allele on bilirubin levels. The presence of 1 or 2 copies of the variant allele resulted in a gene dose effect on total bilirubin levels (table 2). The genetic effect was observed in the absence of treatment and across all treatment groups (figure 1). The overall effect of homozygous *UGT1A1*28* was to increase bilirubin levels by 5.2 μmol/L (0.3 mg/dL), which was less than the increase attributed to the use of ATV or IDV. The simultaneous presence of homozygous *UGT1A1*28* and PI ART containing ATV or IDV resulted in nearly half of the bilirubin levels signaling grade 2 toxicity or greater (figure 1).

Because the models were built on total bilirubin levels, we confirmed the main findings in the restricted data set of 226 measurements of unconjugated bilirubin levels. The estimates for the effect of treatment or genotype on unconjugated bilirubin levels were comparable to those obtained by using total bilirubin levels. Compared with that in individuals who did not receive PIs, the estimated effect on unconjugated bilirubin levels in individuals who received PI ART containing IDV or ATV was an increase of 0.41 (SE, 0.07) $\log_{10}$ μmol/L ($P <$ .001). For PI ART containing LPV, NFV, RTV, or SQV, the effect was estimated to be a decrease of 0.10 (SE, 0.084) $\log_{10}$ μmol/L ($P = .22$). The estimated effect of homozygous *UGT1A1*28* on unconjugated bilirubin levels was an increase of 0.21 (SE, 0.09) $\log_{10}$ μmol/L ($P = .021$). The bilirubin levels reflected the effect of the influences exerted by the antiretroviral drugs and by the genetic background. The estimated total bilirubin level for individuals homozygous for the *UGT1A1*28* allele and who received PI ART containing ATV was 37.7 μmol/L (2.19 mg/dL). The global test for interactions showed only a trend for significance ($P = .062$), and, thus, subcategories contributing to the P value were not screened.

Table 2. Multivariate analysis of the contribution of demographic factors, laboratory parameters, antiretroviral therapy, and *UGT1A1* allelic variants to total bilirubin level.

Variable	Estimated (SE) effect on total bilirubin level, $\log_{10}$ μmol/L	*P*
Reference[a]	0.88	…
Baseline age, per year change	0.00 (0.00)	.808
Male sex	0.03 (0.04)	.452
Chronic hepatitis C or B infection	0.07(0.04)	.042
Longitudinal relationship between hemoglobin (per gram/dL) and bilirubin level	0.02 (0.01)	.002
NRTI ART	0.06 (0.04)	.127
NNRTI ART	−0.20 (0.04)	<.0001
PI ART		
Containing ATV	0.43 (0.03)	<.0001
Containing IDV	0.28 (0.02)	<.0001
Containing LPV	0.06 (0.03)	.031
Containing NFV	−0.07 (0.03)	.024
Containing RTV	0.08 (0.05)	.118
Containing SQV	0.05 (0.03)	.140
*UGT1A1*28* heterozygous	0.07 (0.04)	.072
*UGT1A1*28* homozygous	0.20 (0.05)	<.0001

NOTE. Values are adjusted for all the variables shown and for smoking status and comedications. For continuous variables, the effect on the bilirubin level of each variable represents the impact of a 1-unit increase. For categorical variables, the effect on the bilirubin level represents the impact of the indicated variable compared with the reference value. For non–log-transformed values, refer to the text. ART, antiretroviral therapy; ATV, atazanavir; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir.

[a] The reference value of 0.88 $\log_{10}$ μmol/L (8.8 μmol/L) represents the average bilirubin level for a woman who is 38 years old, is a nonsmoker, has the common *UGT1A1* allele, does not receive ART, does not have hepatitis, and has a hemoglobin level of 13 g/dL.

Twenty-seven participants (28%) had ⩾2 bilirubin levels that were >43 μmol/L (>2.5 mg/dL) (the threshold for jaundice). However, 6 (67%) of 9 participants homozygous for the *UGT1A1*28* allele who received ATV or IDV had bilirubin levels in the jaundice range, versus 4 (7%) of 54 participants with the common allele who did not receive ATV or IDV ($P < .001$) (figure 1).

Overall, 183 (13.2%) of 1386 bilirubin levels were in the jaundice range. We modeled the theoretical impact that establishing a genotyping policy before the initiation of ART would have on jaundice. Figure 2 depicts the estimations from the model, which show that the universal administration of PI ART with ATV or IDV would result in 21.6% of the bilirubin levels being in the jaundice range, whereas genotype-guided ART would result in 5.8% of the bilirubin levels being in the jaundice range ($P < .001$).

DISCUSSION

We quantified the relative contribution of the *UGT1A1*28* allele and different ART combinations to hyperbilirubinemia in HIV-infected individuals. The most relevant finding of the study is the identification of a gene-ART association that could lead to severe hyperbilirubinemia. Individuals with the *UGT1A1*28* allele may develop jaundice when exposed to ATV or IDV. This study was conducted primarily on a white population; however, the allele exists in other populations and is associated with the same physiological effect, which extends the validity of the conclusions to other ethnic groups [24].

We used an objective measurement of bilirubinemia and not a subjective assessment of jaundice to establish the quantitative influence of the various treatments and genotypes. Although hyperbilirubinemia is not a serious adverse effect, clinical jaundice can stigmatize the HIV-infected individual and result in additional consultations and in treatment modification. However, because we wanted to develop a model of drug-gene interaction, our goal was not primarily to assess clinical usefulness but, rather, to present a concept for the use of genetic data in clinics. These results extend the findings of Zucker et al. [16] and O'Mara et al. [25], who documented an association between the *UGT1A1*28* allele and hyperbilirubinemia in individuals who receive PI ART containing IDV or ATV. A genetic predisposition to hyperbilirubinemia has also been reported in individuals undergoing irinotecan treatment for cancer [26]. In contrast, the use of efavirenz resulted in decreased bilirubin levels. This observation is consistent with the known activation by efavirenz of pregnane X receptor [27], which leads to the induction of UGT1A isoforms [28].

The present study explored 1386 measurements of total bil-

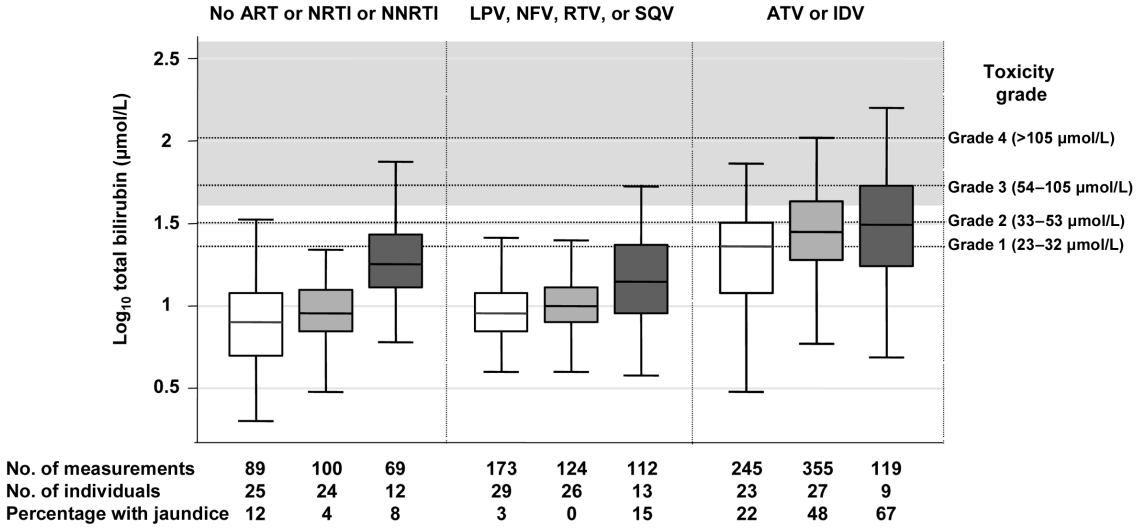

Figure 1. Effect of genotype and antiretroviral therapy (ART) on adjusted total bilirubin levels. Box and whisker plots (median plus interquartile range, upper and lower adjacent values) show the distribution of total bilirubin levels according to *UGT1A1* genotype. Horizontal dotted lines represent the grades of hyperbilirubinemia (grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, serious). The gray interval corresponds to levels resulting in jaundice (defined as >43 μmol/L). Study participants are grouped according to the no. of variant *UGT1A1* alleles (white, homozygous for the common allele; light gray, heterozygous; dark gray, homozygous for *UGT1A1*28*). The no. of measurements of bilirubin levels, the no. of individuals, and the proportion of individuals who had ⩾2 episodes of hyperbilirubinemia in the jaundice range are indicated. ATV, atazanavir; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; RTV, ritonavir; SQV, saquinavir.

irubin levels in 96 participants, during a median follow-up of 6 years. This allowed us to quantitate the precise influence of multiple factors of possible relevance to bilirubin levels (ART regimen, age, sex, hepatitis C and B serostatus, comedication, smoking status, and hemoglobin level) against the genetic background of Gilbert syndrome. The study participants served as their own controls through multiple changes in ART regimens and periods when treatment was not used. We have previously used this longitudinal modeling in the investigation of interactions between apolipoprotein (APO) E and APOC3 and the risk of severe ritonavir-associated hypertriglyceridemia [29].

The frequency of jaundice-range bilirubin levels observed under various treatments and genetic backgrounds allows a preliminary modeling of the potential value of introducing genetic testing before the initiation of ART. We tested the scenario "no genotyping/ATV or IDV as first-line agent" versus "genotype-guided ART" and narrowed the use of ATV or IDV to individuals without the *UGT1A1*28* allele. Implementation of

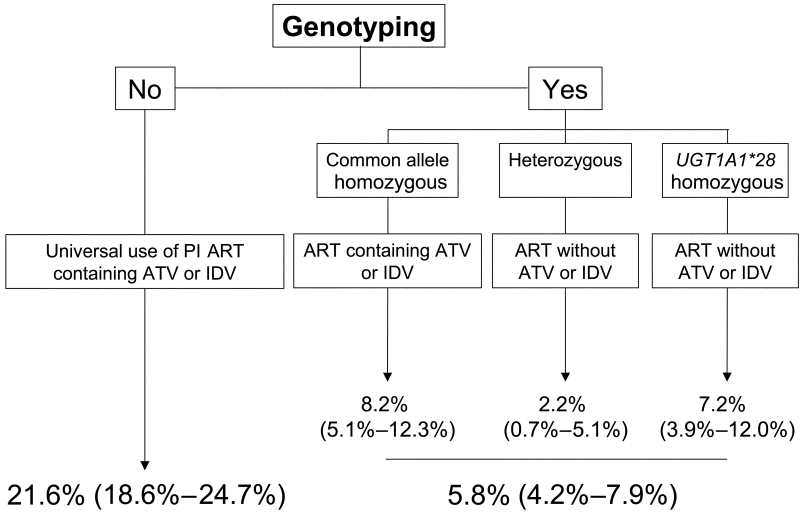

Figure 2. Theoretical impact of establishing a genotyping policy before the initiation of antiretroviral therapy on the proportion (95% confidence interval) of total bilirubin levels >43 μmol/L (>2.5 mg/dL), which is the threshold for jaundice.

such a program would lead to a theoretical 75% reduction in the number of bilirubin levels in the jaundice range. The high frequency of the *UGT1A1*28* allele, and the high risk of developing jaundice in the setting of Gilbert syndrome when exposed to specific PIs, is a good example of how genetic testing for this allele, ideally in conjunction with testing for other markers of toxicity, may be used in the future in the clinical setting.

SWISS HIV COHORT STUDY TEAM MEMBERS

The members of the Swiss HIV Cohort Study are M. Battegay, E. Bernasconi, J. Böni, H. Bucher, P. Bürgisser, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, P. Erb, K. Fantelli, M. Fischer, M. Flepp, A. Fontana, P. Francioli (president), H. Furrer (chairman of the Clinical and Laboratory Committee), M. Gorgievski, H. Günthard, B. Hirschel, L. Kaiser, C. Kind, T. Klimkait, B. Ledergerber, U. Lauper, M. Opravil, F. Paccaud, G. Pantaleo, L. Perrin, J.-C. Piffaretti, M. Rickenbach (head of the Data Center), C. Rudin (chairman of the Mother and Child Substudy), P. Schmid, J. Schüpbach, R. Speck, A. Telenti, A. Trkola, P. Vernazza (chairman of the Scientific Board), R. Weber, and S. Yerly.

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