verse events, such as hyperlipidemia or hyperglycemia, should be discussed before initiation of all protease inhibitor therapy. Importantly, protease inhibitor–associated unconjugated hyperbilirubinemia is not associated with hepatotoxicity and is completely reversible with discontinuation of the protease inhibitor therapy [4, 5]. Therefore, additional consultation should not be necessary in the setting of protease inhibitor–associated hyperbilirubinemia. Furthermore, in large trials, treatment discontinuation for hyperbilirubinemia occurs rarely (<1%) [5, 6].

Rotger et al. do not explore the financial cost of adding genetic screening before antiretroviral therapy initiation, which would be considerable if applied to the entire HIV-infected population. The charge for characterizing the UDP-glucuronosyltransferase 1A1 *(UDPGT1A1)* promoter can be ~$300. Cost-effectiveness analyses are needed to determine the utility of such screening measures. There are limited data on the cost-effectiveness of genetic screening for benign medical conditions in HIV infection or other conditions. In addition to its financial constraints, genetic testing for the $A(TA)_7TAA$ allele is almost completely unavailable in resource-limited settings. The authors also do not discuss the burden of unnecessarily excluding from taking atazanavir or indinavir substantial numbers of individuals who are homozygous or heterozygous for the $A(TA)_7TAA$ allele and will not experience clinical jaundice.

Finally, the authors' statement that the $A(TA)_7TAA$ allele is associated with the same "physiological effect" in nonwhite populations should be made with caution. Data from population studies indicate that jaundice and hyperbilirubinemia are multifactorial in any given subject. For instance, studies have indicated that Asian infants have a higher—and African American infants a lower—incidence of hyperbilirubinemia, compared with their white counterparts [7]. In work referred to by Rotger et al., it was speculated that the prevalence of the $A(TA)_7TAA$ variant *UDPGT1A1* promoter would therefore be highest in Asian subjects, intermediate in white subjects, and lowest in African American subjects [8]. Contrary to this expectation, the $A(TA)_7TAA$ variant was most common among African Americans and least common among subjects of Asian origin [8]. Thus, although there is a relationship between *UDPGT1A1* promoter repeat number and UDPGT1A1 activity (and jaundice) within a racial group, this correlation does not appear to hold across ethnic groups.

In conclusion, although genetic screening offers much promise for decreasing the frequency of adverse events related to medications, we feel that such testing should be reserved for the prevention of serious or irreversible complications. Genetic screening for predisposition to a well-characterized, rapidly reversible adverse event that is not associated with an undesirable medical outcome seems unwarranted.

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Reply to Nettles et al.

To the Editor—Nettles et al.'s [1] comments are consistent with the discussion on the genetic predisposition to unconjugated hyperbilirubinemia in the article by Rotger et al. [2]. However, the mechanism leading to jaundice in newborns that Nettles et al. refer to is not the appropriate example for discussing the genetics of Gilbert syndrome across ethnic groups. In addition, I disagree with 2 of their statements: that stigmatizing a patient is a minor issue as long as the treatment is discontinued and that genetic screening should be reserved for the prevention of serious, irreversible complications.

In the management of a disease that necessitates long-term (lifelong) treatment, "minor" adverse effects are frequent and important [3]. A bout of diarrhea, some nausea, and the occasional jaundice are not to be minimized in importance, in particular when tolerance and toxicity currently constitute the main reasons for treatment discontinuation and change [4].

The cost of genetic testing is rapidly decreasing [5], and our understanding of pharmacogenetics is increasing [6]. This should allow for the development of tests for genetic prediction of toxicity and ef-

ficacy to guide treatment choice among the multiple available antiretroviral drugs. *UGT1A1* is just one of the various genes that could be included in a testing panel. There is limited interest in interrogating any single gene or in aiming analysis at any particular drug.

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Heterosubtypic Immunity to Influenza: Right Hypothesis, Wrong Comparison

To the Editor—We read with interest Epstein's analysis of influenza in Cleveland families [1]. We do not believe that the results convincingly demonstrate heterosubtypic immunity—that is, immunity that is elicited by influenza virus infection and that partially prevents reinfection by different influenza virus subtypes. Epstein's main conclusions are drawn from the difference in influenza attack rates, during the 1957 (pandemic) study year, between children and adults who had had influenza during earlier years (16/29 [55%] vs. 1/18 [6%]; $P = .002$). Yet a strong difference was also observed between children and adults who had not been infected during earlier years (11/66 [17%] vs. 39/75 [52%]; $P < .001$), whereas no difference was noted, in either adults (17% vs. 6%; $P = .28$, Fisher's exact test) or children (55% vs. 52%; $P = .94$), between individuals who had had influenza and those who had not. Our interpretation of these findings is that there was a difference, irrespective of prior exposure, between the attack rate in children and that in adults. This is not surprising [2]. Heterosubtypic immunity to human influenza infection is supported by both biological evidence [3] and epidemiological theory [4, 5], although, in our view, it cannot be deduced from Epstein's comparison of pandemic attack rates in children versus those in adults.

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Reply to Carrat and Lavenu

To the Editor—Carrat and Lavenu comment that the Cleveland Family Study data do not convincingly demonstrate heterosubtypic immunity [1]. My analysis of the subgroup of individuals who had had influenza during the earlier years of that study showed an apparent protective effect of prior illness in adults but not in children; however, my article pointed out that the difference in outcome in adults with such episodes versus those without such episodes was not statistically significant [2, p. 51]. Carrat and Lavenu show this another way, and I accept their point. They and I reached essentially the same conclusion—that "[t]hese historical data alone cannot prove the existence of cross-protection" [2, p. 52]. I felt that the limited data available, although not statistically adequate, were important to describe, for the following reasons:

1. Pandemic influenza caused illness in a 3-fold-lower percentage of adults with prior influenza during the study years than those without (5.6% vs. 16.7%), suggesting an impact of the prior infections, while in children the percentage if anything was slightly higher (55.2% vs. 52.0%). Also note that the overall difference between adults and children in the study population was pronounced only in the pandemic year [2, table 1].
2. The study is valuable for the richness of clinical and laboratory details, and it demonstrates that the low rates of illness in adults were not due to lack of exposure; most of these adults were exposed to the pandemic virus within their own families.
3. These data describe experience during a pandemic; the article does not