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Clinical perspectives on human genetic screening to prevent nevirapine toxicity

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Abstract

Nevirapine is one of the most extensively prescribed antiretroviral drugs worldwide. However, a concern is increased risk for severe toxicity when antiretroviral-naive individuals with higher CD4 T-cell counts initiate nevirapine-containing regimens. Several genetic variants are associated with nevirapine toxicities. The authors used data from a previous study to anticipate potential consequences of genetic screening to prevent nevirapine adverse events. That study enrolled cohorts of African, Asian and European descent in 11 countries, including 276 patients who had experienced severe cutaneous and/or hepatic adverse events with nevirapine-containing regimens and 587 matched nevirapine-tolerant controls. Associations were identified with *HLA-Cw*04*, *HLA-B*35*, *HLA-DRB*01* and *CYP2B6* 516G>T (rs3745274); however, positive predictive values for these genetic markers were low, and most nevirapine-associated adverse events occurred in patients without these markers. Unless better genetic predictors are identified, nevirapine toxicity is best avoided by continuing to follow current prescribing guidelines that are based largely on CD4 T-cell criteria.

Keywords

CYP2B6; HIV; HLA; nevirapine; toxicogenomics

Overview of nevirapine & its pharmacology

The non-nucleoside reverse transcriptase inhibitor nevirapine is one of the most extensively prescribed antiretroviral drugs worldwide. An immediate-release (IR) formulation was first approved for clinical use in 1996 and is now included among the acceptable multidrug regimens as initial therapy for HIV-1 infection in the USA [101]. In resource-limited

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countries, nevirapine was among the first drugs to become generally available for treating HIV-1 infection, and a generic coformulation of IR nevirapine plus two nucleoside analogues continues to be a corner stone of therapy in many countries. In 2011, a once-daily extended-release (ER) formulation of nevirapine was approved for use in combination regimens for treating HIV-1 infection in adults [102]. Nevirapine has played an important role in reducing mother-to-child transmission of HIV-1 globally, with a single intrapartum dose decreasing vertical transmission approximately threefold [1].

Nevirapine has excellent oral bioavailability and distributes widely throughout the body to sites that harbor HIV-1, including the brain. There is considerable interindividual variability in nevirapine pharmacokinetics. For example, in a study of 170 HIV-infected Cambodians, trough plasma nevirapine concentrations at steady-state varied sevenfold, from approximately 2000 to 14000 ng/ml (excluding individuals with who were likely nonadherent) [2]. Inactivation of nevirapine occurs primarily through hepatic CYP2B6 and less so through CYP3A and other isoforms; nevirapine induces its own metabolism (i.e., autoinduction). To decrease the likelihood of rash during treatment initiation, it is recommended that nevirapine be dosed at 200 mg once daily for the first 14 days, then increased to full dose (200 mg twice daily with IR nevirapine, 400 mg once daily with ER nevirapine). Despite the steady-state plasma half-life of approximately 25–30 h of IR nevirapine [103], after the first 14 days it is generally given twice daily owing to concern about possible hepatotoxicity with once-daily dosing [3], although it is not clear that increased plasma nevirapine concentrations cause increased hepatotoxicity. There has been a reported association between nevirapine pharmacokinetics and rash, with 50% higher likelihood of rash for every 20% decrease in plasma nevirapine clearance [4]. The risk of hepatotoxicity with 400-mg once-daily dosing appears to be low when CD4 T-cell thresholds (see below) and 14-day dosage escalation guidelines are followed [5]. One study showed safety of switching from 200 mg twice daily to 400 mg once daily after at least 12 to 18 weeks of therapy [6]. With the ER formulation, 400 mg once daily should begin immediately after the aforementioned 14-day lead in.

Nevirapine toxicity & human genetics

When nevirapine was first approved for clinical use, the predisposition of some individuals to experience severe toxicity was not appreciated, perhaps because those at greatest risk for adverse events (i.e., HIV-infected individuals with higher CD4 T-cell counts) were under-represented in early clinical trials and relatively few HIV-negative individuals receive repeated doses of investigational drugs during Phase I clinical trials. Toxicity became apparent, however, when repeated doses of nevirapine- containing regimens were initiated in HIV-infected patients with higher CD4 T-cell counts [7]. In a clinical trial of the nucleoside analogue emtricitabine (FTC-302 study; Triangle Pharmaceuticals) performed in South Africa, participants with lower plasma HIV-1 RNA concentrations (i.e., higher CD4 T-cell counts) were stratified to receive nevirapine-containing regimens. In that study, 17% of nevirapine recipients experienced grade 3 or 4 liver toxicity, and two died of hepatic failure [7]. The toxicity and other experiences established that higher CD4 T-cell count at nevirapine initiation, female gender and antiretroviral treatment-naive status were associated with increased risk for toxicity [8]. Such data prompted a change in product labeling, recommending that nevirapine-containing regimens not be initiated in adult females with >250 CD4 T cells/mm^3 or in adult males with >400 CD4 T cells/mm^3 [101,103]. Severe hepatotoxicity occurs predominantly among patients with higher CD4 T-cell counts who initiate therapy with plasma HIV-1 RNA <50 copies/ml. Increased risk for toxicity based on CD4 T-cell count thresholds has not been detected in patients with plasma HIV-1 RNA <50 copies/ml who then switch to nevirapine-containing regimens [104].

Before its potential for adverse reactions in immunocompetent individuals was recognized, nevirapine seemed an attractive option as postexposure prophylaxis among HIV-negative healthcare workers following occupational exposures to blood and body fluids. In this setting, nevirapine-containing regimens were generally prescribed for 4–6 weeks. Cases of severe hepatotoxicity, however, occurred when prescribed for postexposure prophylaxis, at least one of which required liver transplantation [9]. This led to nevirapine being contraindicated for use during postexposure prophylaxis [103].

Adverse reactions with nevirapine occur almost exclusively within the first several weeks of therapy and primarily affect the liver and/or skin. Some patients experience only skin and others only liver involvement, while others experience both. Particularly severe reactions tend to be multisystem in nature with concomitant fever, hepatitis, and skin rash (sometimes culminating in Stevens–Johnson syndrome). Early reports of skin rash and fever strongly suggested that many nevirapine reactions were immune-mediated.

A number of studies have sought to identify immunogenetic predictors of nevirapine adverse events. A seminal study from the Western Australia HIV cohort implicated *HLA-DRB1*01:01* in hepatic adverse events [10]. Among 26 patients (25 white patients) who experienced alanine transaminase elevation, fever and/or rash with nevirapine and in 209 controls, *HLA-DRB1*01:01* was significantly associated with hepatic/systemic reactions but not with isolated skin events. The association was only apparent in patients who initiated nevirapine with at least 25% CD4 T cells. More recently, an association was reported between *HLA-DRB1*01:02* and nevirapine-associated hepatic adverse events in the aforementioned protocol FTC-302, which predominantly enrolled black patients [11]. By contrast, studies in Sardinia and Japan implicated *HLA-Cw*08* in hepatotoxicity [12,13].

Regarding nevirapine-associated cutaneous reactions, studies in Thailand implicated *HLA-Cw*04:01* and *HLA-B*35:05* [14,15]. Among 147 patients with such adverse events and in 185 nevirapine-tolerant controls, Chantarangsu *et al.* reported associations with *HLA-B*35:05*, *HLA-Cw*04:01* and the *HLA-Cw*04:01–HLA-B*35:05* haplotype [14]. Similarly, Likanonsakul *et al.* found an association between *HLA-Cw*04* and skin adverse events among 39 patients and 60 controls in Thailand [15].

Few studies have explored relationships between nevirapine toxicity and genes involved in drug metabolism and transport. Regarding hepatic adverse events, analyses of populations from South Africa (i.e., protocol FTC-302) [16], Mozambique [17] and the USA [18] each suggested a very modest association with *ABCB1* (which encodes the membrane transporter P-glycoprotein) position 3435C>T (rs1045642), but not with the *CYP2B6* position 516 G>T (rs3745274) loss-of-function variant that is known to predict decreased plasma clearance of nevirapine [19–21]. As discussed below, only recently has a drug metabolism gene variant been implicated in nevirapine-associated adverse events [22].

A study across patient ancestries & toxicity phenotypes

Inconsistencies among previous genetic association studies of nevirapine may have reflected, at least in part, inconsistent adverse event phenotypes and different geographic regions of ancestry. Results were recently published from a retrospective case-controlled study with prospective DNA collection [22,105]. The study by Yuan *et al.* was designed to separately identify genetic predictors for cutaneous and hepatic adverse events and to separately characterize these associations among cohorts of Asian, European and African descent (hereafter called Asian, white and black patients). Participants were at least 18 years of age, HIV-1 infected, and had a recent CD4 T-cell count of >150 cells/mm^3 within 6 months before starting nevirapine-containing regimens [22]. Patients had experienced severe (grade 3 or 4), symptomatic cutaneous, and/or hepatic adverse events within the first 8

weeks of initiating nevirapine, while controls had tolerated nevirapine for at least 18 weeks. Patients and controls were matched on CD4 T-cell count, gender and self-reported race (for details of study design [22]). The study enrolled 889 participants at 76 research sites in 11 countries, including 276 evaluable patients (175 with cutaneous adverse events and 101 with hepatic adverse events) and 587 evaluable controls. Baseline CD4 T-cell counts were >250 and >400 cells/mm^3 in 70 and 49% of females and males, respectively.

Yuan *et al.* found significant associations between *HLA-Cw*04* and cutaneous adverse events among all study participants, and especially among black and Asian patients [22]. *HLA-B*35* was strongly associated with cutaneous adverse events among Asians (of whom 74% were Thai), but only weakly among white patients. Among Asians the odds ratio for cutaneous adverse events was increased among those carrying both *HLA-Cw*04* and *HLA-B*35*. Regarding drug metabolism and transporter gene variants, associations were noted between *CYP2B6* 516G>T (rs3745274) and cutaneous adverse events among black and white patients, with a weak trend among Asians. Patients carrying both *CYP2B6* 516(rs3745274) TT and *HLA-Cw*04* were at increased risk among the total population and among black and Asian patients analyzed separately. *HLA-DRB1*01* was significantly associated with hepatic adverse events among white patients; however, this allele was infrequent among black patients and rare among Asians. No association was reported between *CYP2B6* 516G>T (rs3745274) and hepatic adverse events or between the previously implicated *ABCB1* 3435C>T (rs1045642) variant [16–18] and either cutaneous or hepatic adverse events. In summary, this study confirmed associations between *HLA-B*35*, *HLA-Cw*04* and skin adverse events previously reported among Thai cohorts [14,15], extended the *HLA-Cw*04* association to black and white patients, confirmed the association between *HLA-DRB1*01* and hepatic adverse events previously reported among white patients [10] and subsequently among black patients [11], and identified a novel association between *CYP2B6* 516G>T (rs3745274) and cutaneous adverse events.

The study by Yuan *et al.* had several limitations [22]. Because cases and controls were matched on CD4 T-cell count, a *post hoc* analysis did not demonstrate a significant contribution of CD4 T-cell count to adverse event risk. Important HLA and non-HLA polymorphisms may have been found with more extensive (e.g., genome-wide) analyses. High-resolution (e.g., four-digit) HLA typing may have increased specificities for at least some associations identified; however, this would probably not have increased sensitivity.

General considerations for human genetic testing in clinical care

All medical disciplines are considering how best to integrate genetic knowledge into clinical care so as to improve health outcomes (i.e., personalized medicine). Many issues regarding logistics and costs of translating any new genetic test into clinical practice are complex. The field will be increasingly influenced (if not driven) by technologic advances in both genomics and medical informatics. For example, in resource-affluent settings, extensive data regarding each patient's genome may soon be housed in their electronic medical record, with informatics-intensive medical decision support being used to inform every prescribing decision. Although to date there are very few situations where human genetic testing is clearly indicated to guide prescribing (e.g., *HLA-B*57:01* screening to prevent abacavir hypersensitivity [23,24,101]), it may soon be routine for patients to have access to vast amounts of data regarding variants in their own genomes. In such a scenario, issues that may now seem daunting related to testing for individual genetic variants may become irrelevant (i.e., assay cost per variant if high-throughput assays are used), or may be addressed across disciplines (e.g., informatics solutions that integrate genomic data into clinical decision-making). However, regardless of such advances, foundational principles to consider risks and benefits of new laboratory tests will still apply.

The utility of any genetic test to inform clinical care depends upon inherent performance characteristics of the test, the prevalence of the condition in the population to whom the test will be offered, and whether the new test substantially improves clinical decision-making over readily available nongenetic information. Of particular relevance to nevirapine, severe adverse events occur almost exclusively among individuals who initiate therapy at higher CD4 T-cell counts and are therefore the patients who may most benefit from genetic screening. Other considerations are availability and relative cost of antiretroviral alternatives to nevirapine. Genetic testing would be most attractive if alternative agents are either unavailable or are cost prohibitive.

In resource-abundant countries, several factors argue strongly against using genetic screening to prevent nevirapine toxicity. Because CD4 T-cell count data are routinely available before initiating therapy, clinicians can readily identify patients with higher CD4 T-cell counts in whom nevirapine should not be initiated. Among such individuals various alternatives are available for nevirapine, including HIV-1 protease inhibitors, integrase inhibitors and other non-nucleoside reverse transcriptase inhibitors. Furthermore, cost differences between nevirapine and some other antiretrovirals are not profound. For example, in 2012 the average wholesale price in US$ for 1 month of therapy (including tenofovir/emtricitabine as the nucleoside component) are as follows: nevirapine-ER US $2060; efavirenz US$2081; rilpivirine US$2196; lopinavir/ritonavir US$2332; raltegravir US$2598; atazanavir/ritonavir US$2961; and darunavir/ritonavir US$3225. Given these considerations and the devastating implications of even a single life-threatening adverse event that could have been avoided, any genetic screening test would have to identify virtually every individual who is predisposed to severe nevirapine-associated reactions (as *HLA-B*57:01* does for abacavir hypersensitivity [23,24]). As discussed below, available data does not support such robust test performance for nevirapine genetic predictors.

In resource-limited countries, many considerations are the same as in resource-abundant countries; however, they may vary by country. Many, if not all, care providers in resource-limited countries have access to CD4 T-cell count data before initiating HIV-1 therapy and can therefore identify patients at greatest risk for nevirapine adverse events. Until recently, WHO guidelines recommended that initiation of HIV-1 therapy be limited to individuals with <200 CD4 T cells/mm^3, with some exceptions. Recent data from Port-au-Prince, Haiti, showing improved outcomes when HIV-1 therapy is started at higher CD4 T-cell counts [25] heightens the potential value of genetic screening for nevirapine. In resource-limited countries, alternatives are available for nevirapine (e.g., efavirenz or lopinavir/ritonavir). However, drug acquisition cost for IR nevirapine may be far less than for protease inhibitors, and there is concern that efavirenz may cause fetal harm during the first trimester of pregnancy [106]. Given these competing concerns, it is conceivable that public health benefits of genetic screening, even with a test that is far from perfect, may be deemed to outweigh individual risks in some resource-limited countries; however, given the challenges in implementing human genetic testing, public health benefits would have to be substantial.

Sensitivity, specificity & clinical consequences of genetic testing with nevirapine

The study by Yuan *et al.* provides empiric data with which to consider the potential utility of genetic screening for nevirapine [22]. Sensitivities and specificities (as well as positive and negative likelihood ratios)of genetic markers of cutaneous and liver adverse reactions from that study stratified by population are shown in Table 1. These markers, either alone or in combination, were not particularly sensitive, and 95% CI bounds around each sensitivity estimate were quite broad. For example, among individuals with cutaneous adverse events, *HLA-Cw*04* was only present in 35, 56 and 34% of Asian, black and white patients,

respectively. Thus two-thirds of Asian and white patients and one-half of black patients with severe cutaneous adverse events lacked *HLA-Cw*04*. Similarly, among individuals with cutaneous adverse events, homozygosity for *CYP2B6 516* TT was only present in 19, 57 and 15% of Asian, black and white patients, respectively. Sensitivities were also low for *HLA-B*35,* either alone or with concomitant *HLA-Cw*04* and for skin adverse events when considering various combinations of *CYP2B6* 516G>T (rs3745274) with *HLA-Cw*04* (latter data not shown). For hepatic adverse events, *HLA-DRB1*01* was similarly insensitive. Only 44% of white patients with hepatic adverse events carried this allele, along with an even lower proportion of Asian and black patients. Specificities for some of these genetic markers were relatively high, at least in part driven by very low allelic frequencies in some populations. Among Asians, the specificity of concomitant *HLA-B*35* with *HLA-Cw*04* was 99%.

While sensitivities and specificities are informative, positive and negative predictive values better describe the potential clinical utility of genetic testing. The matched case-control design used by Yuan *et al.* precludes direct calculation of positive and negative predictive values. This study, however, may be used to estimate these parameters if we make assumptions about population risk prevalence and may provide insight into consequences if genetic testing were to be implemented. To accomplish this we considered hypothetical populations of 1000 individuals, all of whom initiate nevirapine-containing regimens at higher CD4 T-cell counts. Within each population we considered two hypothetical (admittedly, somewhat arbitrary) risk proportions – without genetic screening either 5 or 20% of individuals would experience severe nevirapine adverse reactions (the latter approximates the 17% in protocol FTC-302 [22]). In the vast majority of genetic screening scenarios, not only would the number of missed adverse events far exceed those averted, but the number of patients needlessly avoiding nevirapine would be substantial (Table 2). For example, genetic screening for *HLA-Cw*04* in a hypothetical population of 1000 Asians with a hypothetical 20% likelihood of cutaneous adverse events would prevent approximately 70 cutaneous adverse events; however, approximately 130 cutaneous adverse events would still occur, approximately 211 patients would have to avoid nevirapine and three patients would have to avoid nevirapine unnecessarily for each event prevented. As noted above, there is expected to be little or no benefit of genetic testing among individuals who initiate nevirapine-containing regimens at low CD4 T-cell counts and who are therefore at low risk for severe adverse events.

Conclusion

There are caveats with estimating the utility of genetic screening based on available data. All the above considerations are based on data with IR nevirapine and may therefore not translate directly to the ER formulation. The toxico-genetic association between *CYP2B6* and cutaneous adverse events suggests that nevirapine concentration–time profiles may be relevant [22]. It is therefore possible that some adverse events would be less likely with the new ER formulation, which has a smoother plasma concentration–time profile. The lack of a `gold standard' to confirm which adverse events are definitely caused by nevirapine makes it more difficult to prove clinical benefit of any genetic test. By comparison, for abacavir hypersensitivity reactions, the use of patch testing for immunologic confirmation played an important part in demonstrating the clinical utility of *HLA-B*57:01*. Without abacavir patch testing, the sensitivity of *HLA-B*57:01* for clinically diagnosed hypersensitivity reactions was 45.5%, but increased to 100% with patch testing [23]. Work to identify clinically useful genetic predictors of nevirapine-associated adverse events should continue.

Future perspective

Continued research may identify better genetic predictors of nevirapine adverse events, which could improve positive and negative predictive values accordingly. It would be particularly helpful if genetic variants could predict the most severe, life-threatening adverse events. In this regard, although two individuals died of hepatic failure in protocol FTC-302, there were other individuals in whom transaminase elevations resolved despite continued dosing [7]. A double-blind randomized clinical trial in Thailand is prospectively testing the use of genetic screening to prevent nevirapine-associated cutaneous side effects [107]. If clinically useful genetic predictors of nevirapine-associated adverse events are found, novel strategies to implement genetic testing in resource-limited countries may be warranted.

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Executive summary

Overview of nevirapine & its pharmacology

- Nevirapine is extensively prescribed worldwide to treat HIV-1 infection.
- Nevirapine has excellent oral bioavailability and distributes widely throughout the body.
- Inactivation occurs primarily through hepatic CYP2B6.
- To decrease likelihood of rash, nevirapine is given at half dose for the first 14 days.

Nevirapine toxicity & human genetics

- Nevirapine adverse events primarily affect the liver and/or skin.
- Higher CD4 T-cell count at initiation, female sex and treatment-naive status confer increased risk.
- A study from Australia implicated *HLA-DRB1*01:01* in hepatic events.
- Studies in Thailand implicated *HLA-Cw*04:01* and *HLA-B*35:05* in cutaneous events.

A study across patient ancestries & toxicity phenotypes

- A retrospective study enrolled 276 evaluable cases (175 cutaneous events, 101 hepatic events) and 587 evaluable controls of Asian, European and African descent (hereafter called Asian, white and and black patients).
- For cutaneous events, the study confirmed associations with *HLA-B*35* and *HLA-Cw*04* among Asians, extended the *HLA-Cw*04* association to black and white patients and found a new association between *CYP2B6* 516G>T.
- For hepatic events, the study confirmed the association with *HLA-DRB1*01*.

General considerations for human genetic testing in clinical care

- Several factors argue strongly against genetic screening to prevent nevirapine toxicity.
- Patients at risk can be identified by CD4 T-cell count criteria, and there are alternatives to nevirapine.
- Given the potential severity of nevirapine reactions, genetic screening would have to identify virtually every at-risk patient.
- In resource-limited countries, public health benefits of genetic screening would have to be substantial to warrant implementation.

Sensitivity, specificity & clinical consequences of genetic testing with nevirapine

- The retrospective study mentioned above provides data for considering the utility of genetic screening.
- Genetic markers of cutaneous and hepatic events stratified by population were insensitive.
- High specificities of some genetic markers likely reflect low allelic frequencies.

- With genetic screening, the number of events still occurring would exceed those averted, and many patients would needlessly avoid nevirapine.
- There is no clear benefit of genetic screening at low CD4 T-cell counts.

Conclusion & future perspective

- Continued research may identify genetic markers with better positive and negative predictive values.
- A clinical trial in Thailand is prospectively testing the utility of genetic screening to prevent nevirapine-associated cutaneous side effects.
- If useful genetic predictors are found, strategies to implement genetic testing in resource-limited countries may be warranted.

Table 1

Sensitivity and specificity of *HLA-Cw*04, HLA-B*35, HLA-DRB1*01* and *CYP2B6* screening for nevirapine-associated adverse events[†].

Marker	Population	Patients with marker, n (all cases)	Controls with marker, n (all controls)	Sensitivity, % (95% CI)[‡]	Specificity, % (95% CI)[‡]	Positive likelihood ratio (95% CI)[†]	Negative likelihood ratio (95% CI)[†]
Cutaneous AEs							
*HLA-Cw*04*	Asian[§]	25 (71)	41 (233)	35 (25–47)	82 (77–87)	1.94 (1.53–2.47)	0.78 (0.71–0.88)
	Black	15 (27)	15 (77)	56 (37–73)	81 (70–88)	2.95 (2.44–3.56)	0.54 (0.46–0.64)
	White	26 (77)	58 (277)	34 (24–45)	79 (74–83)	1.62 (1.28–2.05)	0.84 (0.75–0.93)
*HLA-B*35*	Asian	14 (71)	15 (227)	20 (12–30)	93 (89–96)	2.86 (1.96–4.16)	0.86 (0.80–0.92)
	Black	3 (27)	10 (77)	11 (4–28)	87 (78–93)	0.85 (0.55–1.30)	1.02 (0.97–1.08)
	White	21 (77)	48 (277)	27 (19–38)	83 (78–87)	1.59 (1.21–2.09)	0.88 (0.80–0.96)
*HLA-Cw*04* and *HLA-B*35*	Asian	14 (71)	3 (277)	20 (12–30)	99 (96–99.5)	20 (9.51–42)	0.81 (0.75–0.87)
	Black	2 (25)	5 (77)	8 (2–25)	94 (86–97)	1.33 (90.77–2.30)	0.98 (0.94–1.02)
	White	17 (77)	42 (277)	22 (14–33)	85 (80–89)	1.47 (1.08–2.00)	0.92 (0.85–0.99)
CYP2B6 516TT	Asian	10 (52)	20 (222)	19 (11–32)	91 (86–94)	2.11 (1.47–3.03)	0.89 (0.83–0.96)
	Black	13 (23)	11 (53)	57 (37–74)	79 (66–88)	2.71 (2.27–3.25)	0.54 (0.46–0.64)
	White	7 (47)	13 (271)	15 (7–28)	95 (92–97)	3.00 (1.92–4.69)	0.89 (0.84–0.95)
Hepatic AEs							
*HLA-DRB1*01*	Asian	1 (30)	1 (233)	3 (1–17)	99.6 (98–99.9)	7.50 (1.95–29)	0.97 (0.95–1.00)
	Black	2 (14)	8 (77)	14 (4–40)	90 (80–95)	1.40 (0.94–2.09)	0.96 (0.90–1.02)
	White	25 (57)	57 (277)	44 (32–57)	79 (74–84)	2.10 (1.70–2.58)	0.71 (0.62–0.81)

Sensitivity was calculated as (true-positive tests)/(total patients with AEs). Specificity was calculated as (true-negative tests)/(total patients without AEs). Positive and negative likelihood ratios were based on a population of 1000 patients. Positive likelihood ratios were calculated as (sensitivity)/(1−specificity). Negative likelihood ratios were calculated as (specificity)/(1−sensitivity).

AE: Adverse event.

[†]All calculations are based on data in Yuan et al. [22].

[‡]Confidence intervals were calculated with a Bayesian method [26].

[§]Among the Asian population, 74% were Thai.

Table 2

Consequences of *HLA-Cw*04, HLA-B*35, HLA-DRB1*01* and *CYP2B6* screening for nevirapine-associated adverse events[†].

Marker	Population	Positive predictive value, % (95% CI)[†]	Negative predictive value, % (95% CI)[§]	AEs averted per 1000, n (95% CI)[¶]	AEs still occurring per 1000, n (95% CI)	Avoidance of nevirapine per 1000[#], n (95% CI)	Needless avoidance of nevirapine per AE averted, n (95% CI)	Number needed to genotype to avert one AE, n (95% CI)
Hypothetical population in which 5% would have AE without genetic screening: cutaneous AEs								
*HLA-Cw*04*	Asian[†‡]	9.5 (5.4–16.0)	96.0 (95.1–96.9)	18 (13–24)	32 (27–38)	185 (130–236)	10.5 (5.5–18.9)	57 (43–80)
	Black	13.1 (6.1–24.3)	97.2 (95.5–98.4)	28 (19–37)	22 (14–32)	213 (119–308)	7.7 (3.3–16.6)	36 (27–54)
	White	7.8 (4.6–12.2)	95.8 (94.9–96.6)	17 (12–23)	33 (28–38)	216 (168–264)	12.8 (7.5–22.0)	59 (44–83)
*HLA-B*35*	Asian[†‡]	13.6 (5.4–28.3)	95.7 (95.1–96.3)	10 (6–15)	40 (35–44)	73 (42–118)	7.4 (2.8–19.6)	101 (67–167)
	Black	4.3 (0.9–17.4)	94.9 (93.9–96.1)	6 (2–14)	44 (36–48)	129 (68–222)	23.2 (4.9–111.2)	180 (71–500)
	White	7.6 (4.3–13.3)	95.6 (93.9–96.1)	14 (9–19)	36 (31–41)	178 (129–224)	13.1 (6.8–23.6)	73 (53–105)
*HLA-Cw*04* and *HLA-B*35*	Asian	44.0 (13.6–75.9)	95.9 (95.4–96.4)	10 (6–15)	40 (35–44)	22 (9–51)	2.3 (0.6–8.5)	101 (67–167)
	Black	6.1 (0.7–30.5)	95.1 (94.3–96.1)	4 (1–13)	46 (38–49)	66 (29–145)	16.4 (2.3–145.3)	250 (80–1000)
	White	7.1 (3.6–13.6)	95.4 (94.6–96.2)	11 (7–17)	39 (34–43)	155 (109–204)	14.0 (6.6–29.2)	91 (61–143)
CYP2B6 516TT	Asian	10.1 (4.0–21.9)	95.5 (94.8–96.3)	10 (6–16)	40 (34–45)	95 (61–147)	9.9 (3.8–26.8)	104 (63–182)
	Black	12.5 (5.4–24.5)	97.2 (95.2–98.5)	28 (19–37)	22 (13–32)	225 (119–346)	8.0 (3.2–18.7)	35 (27–54)
	White	14.0 (4.4–32.9)	95.5 (94.9–96.2)	7 (4–14)	43 (36–47)	53 (31–89)	7.1 (2.2–25.4)	134 (71–286)
Hypothetical population in which 5% would have AE without genetic screening: hepatic AEs								
*HLA-DRB1*01*	Asian	29.0 (2.6–89.9)	95.1 (95.0–95.8)	2 (1–9)	48 (42–50)	6 (1.4–27)	3.4 (0.2–54.8)	600 (118–2000
	Black	6.7 (1.0–29.6)	95.2 (94.1–96.8)	7 (2–20)	43 (30–48)	106 (49–209)	14.8 (2.4–104.6)	140 (50–500)
	White	10.1 (6.1–15.8)	96.4 (95.4–97.4)	22 (16–29)	28 (22–34)	217 (159–266)	9.9 (5.6–16.6)	46 (35–63)
Hypothetical population in which 20% would have AE without genetic screening: cutaneous AEs								
*HLA-Cw*04*	Asian	33.3 (21.4–47.5)	83.6 (80.4–86.8)	70 (50–94)	130 (106–150)	211 (131–255)	3.0 (1.4–5.1)	14 (11–20)
	Black	41.6 (23.6–60.3)	87.9 (81.6–92.9)	111 (74–146)	89 (54–126)	267 (116–332)	2.4 (0.8–4.5)	9 (7–14)
	White	28.7 (18.8–39.8)	82.7 (79.6–85.8)	68 (48–90)	133 (110–152)	235 (162–276)	3.5 (1.8–5.8)	15 (11–21)
*HLA-B*35*	Asian[†‡]	42.7 (21.4–65.2)	82.3 (80.2–84.6)	39 (24–60)	161 (140–176)	92 (49–141)	2.3 (0.8–5.9)	25 (17–42)
	Black	17.6 (4.3–50.0)	79.7 (76.5–83.8)	22 (8–56)	178 (144–192)	126 (62–230)	5.7 (1.1–28.7)	45 (18–125)
	White	28.2 (17.8–42.2)	82.0 (79.4–84.9)	55 (38–76)	146 (124–162)	193 (128–238)	3.5 (1.7–6.3)	18 (13–26)
*HLA-Cw*04* and *HLA-B*35*	Asian	78.9 (42.9–93.8)	83.1 (81.4–85.0)	39 (24–60)	161 (140–176)	50 (21–85)	1.3 (0.3–3.5)	25 (17–42)
	Black	23.5 (3.4–67.6)	80.3 (77.8–83.8)	16 (4–50)	184 (150–196)	68 (27–161)	4.2 (0.5–40.3)	63 (20–250)
	White	26.7 (14.9–42.9)	81.3 (78.8–84.2)	44 (28–66)	156 (134–172)	166 (107–217)	3.7 (1.6–7.7)	23 (15–36)
CYP2B6 516TT	Asian	34.8 (16.4–57.1)	81.8 (79.4–84.7)	39 (22–64)	162 (136–178)	111 (63–169)	2.9 (1.0–7.7)	26 (16–45)
	Black	40.5 (21.4–60.7)	87.9 (80.7–93.1)	113 (74–148)	87 (52–126)	279 (115–365)	2.5 (0.8–4.9)	9 (7–14)
	White	43.7 (17.9–70.0)	81.7 (79.8–84.3)	30 (14–56)	170 (144–186)	68 (34–116)	2.3 (0.6–8.3)	34 (18–71)
Hypothetical population in which 20% would have AE without genetic screening: hepatic AEs								
*HLA-DRB1*01*	Asian	66.0 (11.1–97.7)	80.5 (79.8–82.8)	7 (2–34)	193 (166–198)	10 (2–50)	1.5 (0.1–24.8)	150 (29–500)

Marker	Population	Positive predictive value, % (95% CI)[†]	Negative predictive value, % (95% CI)[§]	AEs averted per 1000, n (95% CI)[¶]	AEs still occurring per 1000, n (95% CI)	Avoidance of nevirapine per 1000[#], n (95% CI)	Needless avoidance of nevirapine per AE averted, n (95% CI)	Number needed to genotype to avert one AE, n (95% CI)
	Black	25.6 (4.8–66.7)	80.7 (76.9–86.4)	29 (8–80)	171 (120–192)	112 (45–237)	3.9 (0.6–29.6)	35 (13–125)
	White	34.8 (23.5–47.1)	85.0 (81.3–88.7)	88 (64–114)	112 (86–136)	252 (156–286)	2.9 (1.4–4.5)	11 (9–16)

This table considers hypothetical populations of 1000 individuals, all of whom initiate nevirapine-containing regimens at higher CD4 T-cell counts. Within each population hypothetical scenarios were examined in which, without genetic screening, either 5 or 20% of individuals would experience severe nevirapine adverse reactions and in which, with genetic screening, those with the risk allele would be prescribed an antiretroviral other than nevirapine.

AE: Adverse event.

[†]All calculations are based on data in Yuan et al. [22].

[‡]Positive predictive value was calculated as ([number of individuals per 100 that would have the AE without genetic testing] × [genetic test sensitivity])/([number of individuals per 100 that would not have the AE without genetic testing] × [1−(genetic test specificity)]).

[§]Negative predictive value was calculated as ([number of individuals per 100 that would not have the AE without genetic testing] × [genetic test specificity])/([(number of individuals per 100 that would not have the AE without genetic testing) × (genetic test specificity)] + [(number of individuals per 100 that would not have the AE without genetic testing) × (1-genetic test sensitivity)]).

[¶]Number of nevirapine-associated AEs that would be prevented by genetic screening; AEs still occurring: number of nevirapine-associated AEs that would still occur (i.e., among individuals without the genetic marker); avoidance of nevirapine: number of individuals who would be prescribed an antiretroviral other than nevirapine; needless avoidance of nevirapine: for each nevirapine-associated AEs prevented, how many individuals would receive a different antiretroviral but could have safely received nevirapine.

[#]Avoidance of nevirapine (per AE averted) was calculated as ([number of AEs that would occur per 1000 if genetic testing were not done] × [genetic test sensitivity/([(1 −genetic test specificity) × (1000 × [number of individuals per 100 that would not have the AE without genetic testing])/100]).

[††]Among the Asian population, 74% were Thai.