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Should abacavir be a first-line alternative for adults with HIV in sub-Saharan Africa?

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Abstract

Despite a poor toxicity profile, zidovudine supersedes abacavir as an alternative first-line agent in most international treatment-guidelines due to concerns about HLA-B*57:01-related abacavir-hypersensitivity. We detected one case of HLA-B*57:01 carriage among 513 HIV-infected individuals in Uganda, which, in combination with prior reports, supports the safety of abacavir in the region.

Keywords

Uganda; Africa; HIV; antiretroviral therapy; HLA-B*57:01; abacavir

Introduction

Abacavir (ABC) is a nucleoside reverse transcriptase inhibitor for treating HIV-infections. It is a key element of first-line antiretroviral therapy (ART) regimens recommended by the United States Department of Health and Human Services (DHHS). Yet, a major limitation to ABC usage is its association with a potentially fatal immunologically mediated hypersensitivity reaction in patients within the first six weeks of treatment [1]. The multinational PREDICT-1 and US-based SHAPE studies confirmed the presence of a specific human leukocyte antigen (HLA) type, HLA-B*57:01, as the primary risk factor for

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Authors contribution: The study was conceptualized and designed by GQL, SMM, JEH and MJS. Plasma samples, baseline and follow-up data were collected and managed by YB, PWH, JNM, and DRB. HIV-1 genotyping laboratory work was done by GQL. Results were analyzed by GQL, SMM and MJS. GQL, SMM and MJS wrote the manuscript; all authors contributed to, seen, and approved the manuscript.

ABC-associated hypersensitivity reactions, with a sensitivity of 100% in both white and black races [2,3]. Frequency of HLA-B*57:01 is approximately 8% among Caucasians and 2.5% among African-American in the United States [4]. To protect against this reaction, the DHHS recommends HLA-B*57:01 screening before starting patients on an ABC-containing regimen [5].

However, data from sub-Saharan Africa, where over 70% of the world's population with HIV resides, are scarce. Moreover, HLA-B*57:01 testing is not available in much of the region. As such, a notable difference between US and World Health Organization (WHO) Guidelines is that WHO recommends use of zidovudine (AZT) in place of ABC as an alternative first-line therapy in adults who cannot tolerate tenofovir (TDF) [6], despite known toxicities associated with AZT use [7]. ABC does remain a primary component of alternative first-line regimens for adolescents and a preferred agent for children below 10 years old [8]. In an effort to compare ART regimens in children, the CHAPAS-3 study compared ABC with two other nucleoside reverse transcriptase inhibitors (stavudine, AZT), and concluded all three drugs had low toxicity and good clinical, immunological, and virological responses. They also found no hypersensitivity reactions among 165 Zambian and Ugandan children <13 years old receiving ABC without genotyping for HLA-B*57:01 [9]. The DART/NORA study demonstrated a similarly low rate of hypersensitivity reactions in Ugandan adults receiving ABC (6/300, 2%), although none of the six patients carried the HLA-B*57:01 allele [10].

Consequently, an important question for the field is whether ABC should replace AZT as a first-line alternative for adults, even in the absence of HLA-typing. ABC use is likely to become more common in sub-Saharan Africa with increasing availability of ART and with chronic complications of AZT and TDF-based regimens such as anemia and renal toxicity. Because previous studies on the prevalence of HLA-B*57:01 in the region are rare and have small samples, further data are needed to further support the safety of ABC use more broadly. We conducted HLA typing in 581 HIV-infected patients in Kampala (n=81) and Mbarara (n=500), representing one of the largest HLA-typing efforts in sub-Saharan Africa. Here, we report the prevalence of HLA-B*57:01 in this population, and review the literature on HLA-B*57:01 testing, with the goal of providing a summary of the current knowledge on the safety of ABC use in the region.

Methods

Cohort Description

The Uganda AIDS Rural Treatment Outcomes (UARTO, NCT0159632) pilot study enrolled 81 subjects in Kampala between 2002–2004. The main study enrolled treatment-naïve HIV-1 infected subjects in care at the Immune Suppression Syndrome (ISS) Clinic in Mbarara, Uganda, a rural community 270 kilometers southwest of Kampala [11–13]. Participants were enrolled just prior to the start of ART, and were longitudinally monitored with study visits approximately every three months. Infections were predominantly subtype A1 (49%) and D (43%) [14]. The first 581 subjects enrolled underwent HLA-typing.

Ethical Considerations

All patients provided written consent. The study and material/data transfer was approved by the Mbarara University of Science and Technology Human Subjects Committee (14/01-03), the Uganda Council for Science and Technology (HS 07, HS 938), Partners Healthcare Human Subjects Committee (2011P000522), the University of British Columbia/Providence Health Care Research Ethics Board (H11-01642), the University of California Human Research Subjects Committee (10-03457), and the Frederick National Laboratory for Cancer Research (IRB 3314). Samples used were anonymized and coded with subjects' unique research identification numbers and shipped from Uganda to University of California San Francisco, then routed to Frederick National Laboratory for Cancer Research for HLA-typing. Data was coded in password-locked files and transferred to investigators at BC Centre for Excellence in HIV/AIDS and Partners Health Care for downstream analyses.

Laboratory procedures/methods

EDTA buffy coats containing one to three million cells per sample in 1.8 ml CryoTube vials (Thermo Fisher Scientific, Roskilde, Denmark) were shipped from Uganda to USA on dry ice and stored in a −80ºC freezer. DNA was prepared using the QIAamp DNA Blood Midi Kit (Qiagen Sciences Inc, Germantown, MD, USA) following manufacture's protocols. HLA typing was performed using Roche 454/Fluidigm HLA Typing Kits following the Roche protocols [15]. Briefly locus-specific primers were used to amplify 14 polymorphic exons of HLA-A, B, C, DPB1, DQA1, DQB1 and DRB genes with Fluidigm Access Array (Fluidigm Singapore PTE Ltd, Singapore). The 14 Fluidigm PCR amplicons were pooled and subjected to sequencing on a 454 FLX Genome Sequencer (454 Life Sciences Corporation, Branford, CT, USA). HLA alleles and genotypes were called using the Conexio ATF 454 HLA typing software (Conexio Genomics Inc, Perth, Australia).

Study design/data analyses

Samples from 52 individuals in Kampala, and 461 individuals in Mbarara yielded successful HLA-B genotyping results. All were included in subsequent analysis. Results were stored and analyzed in 4-digit resolution. HLA-B*57:01 allele frequency was defined as occurrence divided by total patient number times two, and carriage frequency was the number of patients carrying HLA-B*57:01 (homozygous or heterozygous) divided by the total number of patients sampled. No additional software was used.

Results

Patient Characteristics

In the UARTO pilot study (Kampala), 62% participants were female. Median age was 36 (IQR 30–40), baseline $\log_{10}$ viral load was 5.5 copies/mL (IQR 4.9–5.8), and baseline CD4 count was 60 cells/μL (IQR 12–136). All pilot study participants initiated a regimen of stavudine (d4T), lamivudine (3TC) and nevirapine (NVP). In the main cohort (Mbarara), 70% of participants were female, median age was 35 (IQR 29–39), baseline log10 viral load 5.1 copies/mL (IQR 4.7–5.6), and baseline CD4 count 131 cells/μL (IQR 74–197). Initial regimens were primarily NVP (86%) and efavirenz (EFV)-based (12%) with a combination

of nucleoside reverse transcriptase inhibitors (lamivudine with zidovudine, tenofovir, stavudine, or abacavir).

Prevalence of HLA-B*57:01 and ABC usage in UARTO

HLA-B*57:01 was not observed in the 52 Kampala subjects. In the main Mbarara cohort, one subject was heterozygous for HLA-B*57:01 among 461 subjects (0.2% prevalence). This subject did not receive ABC during study observation from 2006 – 2011. During the entire follow up duration from 2005–2015 in Mbarara, only two other patients ever-used ABC (0.4% usage rate); neither had HLA-B*57:01. No clinical hypersensitivity reactions were documented by self-report.

Literature Review

To compare our reported prevalence with prior publications, we performed a literature review of existing reports on the prevalence of HLA-B*57:01 in sub-Saharan Africa. Two relevant studies [16,17] were identified at www.allelefrequencies.net [18,19]. A Pubmed search returned 303 studies containing search terms “(HLA AND 57:01) OR (HLA AND “57:01”).” Manual screening returned three relevant studies with primary data pertaining to adult African populations [10,20,21]. Collectively, the five studies included a total of 1,812 individuals; HLA-B*57:01 allele frequency ranged from 0–3% (Table 1).

Discussion

The UARTO cohort represents one of the largest HLA genotyping studies conducted in sub-Saharan Africa. We detected only one case of HLA-B*57:01 carriage (0.2%) among 513 patients tested in an urban mixed ethnicity area (Kampala) and a rural, more homogenous setting in the southwestern region of Mbarara, Uganda.

Our data are largely in agreement with prior estimates in the region (Table 1). Prior studies from Uganda, Kenya, Zambia, and Guinea-Bissau documented similarly rare allele prevalence rates at or less than 1% [10,16,17]. A singular exception comes from a study in Kampala, Uganda which demonstrated an allele prevalence of 3% [16]. Notably, this study is the only one in the region (or Kampala, of which there are two others) with a prevalence over 1%, and remains well below that seen in Caucasian and Asian populations elsewhere [18,19]. Taken together, the vast majority of data do suggest a low risk for ABC hypersensitivity in the region, despite the lack of availability of HLA-B*57:01 screening.

Currently, ABC-based ART is not included as part of recommended first-line regimens for adults in the WHO HIV treatment guidelines. AZT-based ART is recommended as an alternative for participants with an intolerance or contraindication to TDF [6]. Although there is little access to HLA-B*57:01 screening in sub-Saharan Africa, there are significant risks with AZT-based regimens as well. Due to these concerns, AZT-based ART was downgraded in the United States DHHS and European AIDS Clinical Society guidelines from recommended first-line to alternative first-line regimens [22,23]; and most recently, AZT-based ART has been removed from the list of first-line regimens altogether [24,25].

The CHAPAS-3 study demonstrated that ABC and AZT had comparable virological and immunological efficacy, and similar adverse effect frequencies in children [9], supporting the use of either in that patient population. However, several other studies have highlighted significant toxicities associated with longer term AZT use, including bone marrow suppression (severe anemia and neutropenia) [26–29], lipodystrophy [27,28,30–32], gastrointestinal side effects [33], and other metabolic complications [27,28]. In addition, the GlaxoSmithKline CNA30024 study showed that AZT-based ART was inferior to ABC-based ART with regards to CD4+ T-cell response in adults [33]. ABC and TDF-based regimens also provide the benefit of once daily dosing, as opposed to twice daily dosing for AZT. Finally, in contrast to ABC and TDF, AZT has not been studied with integrase strand transfer inhibitors (INSTIs) such as dolutegravir [34,35], which are now a preferred component of first-line regimens in the US and Europe [22].

Despite these factors supporting the use of ABC over AZT as an alternative to TDF in first-line regimens, several additional considerations must be taken into account. First, it is unlikely that pre-treatment HLA-B*57:01 testing will be carried out in resource-limited settings. Careful patient monitoring after ABC initiation should be encouraged in such settings to monitor for hypersensitivity reactions and to appropriately switch patients in the correct clinical scenario. Second, drug resistance testing remains rare in resource-limited settings, and both transmitted and acquired drug resistance are increasing in the sub-Saharan African region [36–38]. The possibility of the presence of M184V, a common drug resistance mutation [14,39–41] which decreases activity of ABC but increases susceptibility of AZT, should be considered before selecting ABC over AZT, particularly in those failing a first line regimen containing 3TC or emtricitabine. Third, although data are conflicting [42–48], the D:A:D cohort study has repeatedly demonstrated associations between recent ABC use and risk of myocardial infarction [45–47], resulting in a relative contraindication to ABC use for patients with prior or high risk of cardiovascular disease [5]. Lastly, although generic versions of ABC and AZT are generally similar in cost [49], the implications of widespread ABC use from both the system and individual perspectives need to be considered as part of large scale guideline changes.

Our study has important limitations. We had a relatively small sample size in Kampala, although prior studies have also demonstrated low prevalence of HLA-B*57:01 in that city. Future large-scale HLA-typing studies including both urban and rural African communities will provide a better estimate of HLA-B*57:01 prevalence. This should be forthcoming with the ongoing H3 Africa studies, which aim to conduct genetic testing in large, diverse African populations [50]. Our study also lacks ABC-associated hypersensitivity data, so we were unable to fully exclude the possibility of non-HLA-B*57:01 associated hypersensitivity reactions. Because not all cases of ABC-association hypersensitivity reactions have been associated with the HLA-B*57:01 allele, as demonstrated in the Ugandan DART/NORA study in which six presumed cases were HLA-B*57:01 negative [2], other factors or alleles might be involved in this population. Therefore, despite the low prevalence of HLA-B*57:01 in the region, patients initiating ABC should still be carefully monitored for potential hypersensitive reactions.

In conclusion, our data suggest a role for considering ABC as an alternative first-line agent in those who cannot tolerate TDF. We found very low prevalence of HLA-B*57:01 carriage in two regions of the country, similar to previous studies in the region. Because ABC leads to superior immunologic recovery, it has a once-daily dosing schedule, and it has been studied as a component of regimens containing INSTIs, future guidelines in sub-Saharan Africa might consider elevating ABC to a potential alternative first-line option in settings where regional HLA prevalence is available and/or clinicians can carefully monitor patients during the first weeks of therapy.

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Table 1

Published data on HLA-B*57:01 prevalence and ABC-associated hypersensitivity reactions in sub-Saharan African populations

Publication Year	Country	Region/Ethnicity	Sample size	Allele frequency	Carriage frequency	Received ABC?	ABC hypersensitivity reaction rate	References	
2004	Kenya	Nandi	240	0.0083	NA	No	NA	Cao, 2004	[16]
	Kenya	Luo	265	0.0076	NA	No	NA		
	Mali	Dogon	138	NA	NA	No	NA		
	Uganda	Kampala	161	0.0311[b]	NA	No	NA		
	Zambia	Lusaka	44	0.0114	NA	No	NA		
2005	Guiné-Bissau [c]	NA	65	0	NA	No	NA	Spínola, 2005	[17]
2011	Uganda	Kampala, Entebbe	300[a]	0	NA	Yes	6/300 (2%)	Munderi, 2011	[18]
2014	South Africa	Northern region	206	0	NA	No	NA	Masebe, 2014	[19]
2014	South Africa	Black	196	0	0	No	NA	Loubser, 2014	[20]
		Caucasian	97	NA	0.082	No	NA		
		Indian	50	NA	0.12	No	NA		
		Mixed	50	NA	0.08	No	NA		
2016	Uganda	Kampala	52	0	0	No	NA	This study	
		Mbarara	461	0.001	0.002	No	NA		

[a] n=300 received ABC; n=247 after adjusting for loss to follow up

[b] 0.02 < allele frequency < 0.05

[c] Guiné-Bissau samples belonged to seven different ethnic groups: Balanta (n = 10), Papel (n = 11), Mandinga (n = 9), Felupe (n = 5), Bijagós (n = 10), Fula (n = 10), and Mancanha (n = 10)