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Tolerance and Durability of Abacavir/Lamivudine (ABC/3TC) Containing Regimens: Results from a large French Prospective Cohort

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Abstract

Background: Abacavir is considered as a potent and well tolerated drug but recent controversial data have raised questions concerning cardiovascular tolerability and virological efficacy in antiretroviral initial regimen with abacavir/lamivudine (ABC/3TC).

Methods: Patients were selected from the Dat'AIDS french prospective cohort if they were prescribed a regimen containing ABC/3TC free or fixed dose combination for the first time between 01/01/2004 and 31/12/2007 before HLA screening recommendation or routine usage. All causes of treatment discontinuation were recorded, as well as immuno-virological and clinical data during follow-up.

Results: Among the 1704 patients included in the study (male 69%, mean age 43 years) 407 (24%) were antiretroviral naïve, 696 (41%) had viral load (VL) below detection on ARV treatment (switch), and 601 (35%) were on treatment with detectable VL (failure) at time of ABC/3TC initiation. Overall 565 patients (33%) discontinued ABC/3TC combination during follow-up, among them 26% have used ABC in the next regimen. Reasons for discontinuation were intolerance in 14% of the cases - including suspected hypersensitivity (HSR) in 7% of the overall population - treatment failure in 20%, and other causes in 39%. The median time to treatment discontinuation was 52 months for the overall population. After 2 years, the probability of receiving ABC/3TC was at 62%, 77%, and 60% respectively for the defined groups. Finally, the VL on treatment was below detection for 86%, 90%, and 71%, respectively.

Conclusion: In this population ABC/3TC containing regimens were maintained with virological success for more than 2 years. Tolerance issues including HSR were the main reason for early discontinuation.

Keywords: HIV; Abacavir; Lamivudine; Antiretroviral therapy; Durability; Tolerance

Introduction

Abacavir (ABC) has been used as part as combined therapy (cART) in human immunodeficiency virus type 1 (HIV-1)-infected patients since 1998 and thus has contributed to the large improvements in patients' health and survival [1]. Fixed drug combination with lamivudine (3TC) provided benefits in adherence to treatment by reducing the daily pill burden. Severe cases of drug related hypersensitivity were described with a frequency of 4 to 7% [2], later associated with a positive HLA-B*5701 aplotype [3], allowing efficient screening of 'at-risk' patients. ABC has been associated with an increased risk of myocardial infarction (MI) in observational studies [4] but more recently, this has been refuted in further analyses [5,6]. Although ABC has been proven potent in many studies, it may be less effective in patients with baseline viral load over 5 $\log_{10}$ copies/mL and some expert guidelines have limited its use, despite European and US health authorities have not limited ABC/3TC prescription in high viral load [7]. However, every antiretroviral drug (ARV) has its own profile of tolerability and the choice of treatment should always be personalized, taking into account the overall absolute risks and benefits for long-term treatment. Many physicians believe that abacavir is a potent drug and long term tolerance has to be documented.

In order to describe tolerance and durability of cART based on the combined ABC/3TC, we searched our large prospective cohort for

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ABC naïve patients who have been receiving this combination as part of one of their regimens.

Materials and Methods

Information was collected from 7 large HIV reference centers in France (Fort-de-France, Marseille, Nantes, Nice, Paris, Toulouse, and Tourcoing). These hospitals maintain prospective cohorts of all HIV-1 infected patients who seek care in the centers and provided written informed consent. The cohorts are implemented via an electronic medical record (EMR). The patients enter the cohort when they seek care in one of the centers regardless of their HIV disease history and all previous clinical events as well as therapeutic history are collected with appropriate dates. The EMR collects demographic details, clinical events, antiretroviral history, viral load and CD4 cell count data for patients at regular 3-6 month intervals during routine clinical assessment. This system allows use of the databases with minimal delay, limited to automatic and manual quality controls performed before any analysis [8].

For the purpose of this study, we selected adult HIV-1 infected patients' naïve for ABC who have been receiving for the first time ABC and 3TC either as a fixed-dose combination or a separate component between January 2004 and December 2007 as part of their regimen, irrespective of their previous therapeutic history. The patients could have received 3TC. ABC/3TC combination may be used either as part of the first antiretroviral regimen (naïve patients), as part of a switch strategy in patients with HIV-1 RNA level (VL) below 50 copies/ml (switch) or, as part of a salvage regimen in patients with a previous failing regimen (failure). The ABC/3TC fixed-dose combination has been available from January 2005.

We recorded demographical (age, sex), biological (all available CD4 and VL values during follow up, hepatitis co-infections), therapeutic (treatment history, ARV drugs prescribed in association with ABC/3TC) and clinical data (duration of known infection, all major clinical events - including pregnancies - before or during treatment, death with date and cause if any). In case of ABC/3TC discontinuation, the date and cause were recorded. The cause recorded in the data base is coded at the time of discontinuation by physician who makes the decision with the patient, following a limited list of items. Causes of discontinuation were classified as intolerance (any adverse event leading to discontinuation), virological failure (detectable VL) or other cause (non-adherence, pregnancy, inclusion in a clinical trial, as examples). If the VL was greater than 50 copies/mL at the time of discontinuation, the cause was considered as virological failure whatever the recorded cause in the database. At the time of first prescription and for most of the patients, determination of HLA-B haplotype was not available in routine practice. "Clinical hypersensitivity" as defined by the physician, as well as "cutaneous intolerance" and "treatment intolerance" was all considered as suspected HSR. If a patient died while taking ABC/3TC, the date of death was recorded as date of discontinuation. The cause of death was collected for each patient. In the event of unknown cause of death, it was considered as potentially related with a major cardio-vascular event (CVE). Major CVEs were defined as myocardial infarction, stroke, and surgery for coronary artery disease or un-witnessed death. Minor events were defined as peripheral vascular disease, congestive heart failure or drug treatment for coronary artery disease. All CVEs recorded while a patient was receiving ABC/3TC were analyzed regardless of their severity. Virological success was defined as a VL below 50 copies/mL.

All analyses were carried out on the overall population and in the 3 defined groups (naïve, switch and failure). Categorical variables were described by frequencies and numerical variables by distribution (median, 25 and 75% percentiles). Time to treatment discontinuation was analyzed by the Kaplan Meier survival method. Follow-up was censored if the patient stopped taking ABC/3TC, died or at the censoring date (31 may 2008) whichever occurred first. If the patient was lost to follow up, the last date of medical visit was considered as date of last news. Statistical analyses were performed with the use of SAS software version 9.1 (SAS Institute, NC, and USA).

Results

We identified 1704 patients who responded to the selection criteria. ABC/3TC was used as part of the first regimen for 407 patients

	Naïve patients (N=407)	**Switch (N=696)**	**Failure (N=601)**	**Total (N=1704)**
Sex, N (%) men	295 (72.5)	483 (69.4)	398 (66.2)	1176 (69)
Age, median [Q1-Q3] years	41 [23.5-48]	44 [38-50]	42 [36-48]	43 [36-49]
Lenght of known infection, median [Q1-Q3] years	2 [0.3-7.8]	9.2 [4-14.6]	11.5 [6.6-16]	8.7 [2.9-14.5]
Hepatitis co-infection, N (%)	83 (20.4)	161 (23.1)	167 (27.8)	411 (24.1)
Previous CDC class C event, N (%)	85 (20.9)	209 (30)	179 (29.8)	473 (27.8)
Baseline VL, median **[Q1-Q3] $\log_{10}$ copies/mL**	4.8 [4.1 – 5.3]	1.6 [1.6 – 1.6]	3.9 [2.6 – 4.8]	2.5 [1.7 – 4.5]
Patients with baseline VL ≥ 5 $\log_{10}$ copies/mL (%)	41.2	-	18.5	15.1
Baseline CD4 cells/mm³, median [Q1-Q3]	239,2 [111-319]	512,4 [345-670]	286 [167-456]	354,7 [211-558]
Baseline CD4 cells <200/mm³ (%)	40.4	8.1	30.8	23
Nadir CD4 cells/mm³, median [Q1-Q3]	222 [104-289]	177 [71-264]	174 [64-261]	184 [74-272]
Number of previous regimens, median [Q1-Q3]	-	3 [1-5]	3 [2-5]	3 [3-5]
Treatment strategies				
3 drugs in the regimen, N (%)	373 (92)	664 (95)	485 (81)	1522 (89)
ABC/3TC + 1 NNRTI, N (%)	36 (9)	241 (35)	49 (8)	326 (19)
ABC/3TC + 1 bPI, N (%)	211 (52)	279 (40)	301 (50)	791 (46)
ABC/3TC + AZT, N (%)	119 (29)	115 (16)	117 (19.5)	351 (21)
Other, N (%)	7 (2)	29 (4)	18 (3.5)	54 (3)
4 drugs or more in the regimen, N (%)	32 (8)	26 (4)	113 (19)	171 (10)

"Naïve patients": ABC/3TC used as part of the first regimen, "switch": as part of a switch strategy in patients with VL below detection, "failure" as part of a rescue regimen in patients with a previous failing regimen; VL=viral load

Table 1: Patients characteristics at baseline.

(naïve group), as part of a switch strategy in 696 patients with VL below detection) and as part of a salvage regimen in 601 patients with a previous failing regimen (failure). Patients were men in 69% of the cases, median age 43 years, with 23% of the population over 50 year-old. Population characteristics at baseline are shown in Table 1. ABC/3TC fixed dose combinations were used in 78% of the patients, the median CD4 cell count was lower in the naïve population (239 cells/mm^3) than compared to the other groups and 41% had a median viral load above 5 $\log_{10}$ copies/mL. The regimen contained 3 drugs in 92% of the naïve, 95% of the switch and 81% of failure groups. A boosted PI was the 3rd agent associated with ABC/3TC in 46% of the overall population, 52%, 40% and 50% respectively in the naïve, switched and failure population (details on the treatment regimen are shown in Table 1).

Among all the population (n=1704), the median time to treatment discontinuation using the Kaplan Meier survival method was 52 months with differences related to the reason for discontinuation (Figure 1). After 2 years of follow up, 62%, 77% and 60% of the naïve, switch and failure population respectively were still taking ABC/3TC.

Overall, 565 treatment discontinuations were recorded (33% of the population). In the naïve, switch and failure populations, the proportions were respectively 36%, 24% and 42%. Median time [IQR] before discontinuation was respectively 4 [1.1-10.2], 4.8 [1.1-13.8] and 7.3 [1.2-17.7] months in the naïve, switch and failure populations (p=0.067). Details of reasons for discontinuation are shown in Table 2. Consistently across the groups, the most frequent reason for discontinuation was intolerance representing 14% of the total population (14%, 13%, and 15% of the naive, switch and failure populations). HSR was clinically suspected in 4% of the patients. Most discontinuations for tolerability reasons (respectively 84%, 75%, and 74% across the groups) occurred during the first 6 months. In the event of suspected HSR, median time before discontinuation was of 17 days [10-33] and for the other tolerability reasons the median time was more than 3 months. No difference in frequency of treatment discontinuation for tolerance was described depending on the other drugs contained in the regimen: 13% of the 791 patients receiving a ritonavir boosted protease inhibitor (bPI) and 12% of the 326 patients receiving a non nucleosidic transcriptase inhibitor (NNRTI). Among the treatment naïve population, discontinuation for virological failure was recorded in 5 (3%) patients out of the 168 with VL ≥ 5 $\log_{10}$ copies/ml and in 11 (4.6%) of the 239 others patients. After ABC/3TC regimen discontinuation, ABC was found in the subsequent regimen for 26% of these patients.

Death was recorded in 27 patients: 9 were AIDS related, 6 due to an end stage liver disease, 6 to cancers, 1 to myocardial infarction, 1 to neurological vascular event, 1 to car fatality and 3 of unknown causes.

A CVE was recorded in 58 patients out of the overall population. Out of these, 21 patients presented a major CVE so the calculated incidence was 8/1000 patients-year - including 12 myocardial infarctions, incidence 5/1000 patient-year. Among these 21 patients, 20 were male with a median age 49 years, 5 had a previous CVE in their medical history, 1 died due to myocardial infarction and 3 were un-witnessed deaths, viral load was below detection for 12, 2 patients were receiving ABC/3TC as part as their first regimen, 13 had been receiving ABC/3TC for more than 1 year, 20 had been treated with a PI-containing regimen before the major CVE occurrence and 4 had a detectable viral load and 581/mm^3 CD4 cells count before the event.

Proportions of patients with virological success at different time points are shown in Figure 2. After 2 years, 86%, 90%, and 70% of the naïve, switch and failure groups, respectively had a viral load below 50 copies/mL. The virological success in the naïve group according to viral load <or> 5 $\log_{10}$ copies/mL tends to show a lesser response in the group of patient with a high viral load. The results are in line with what

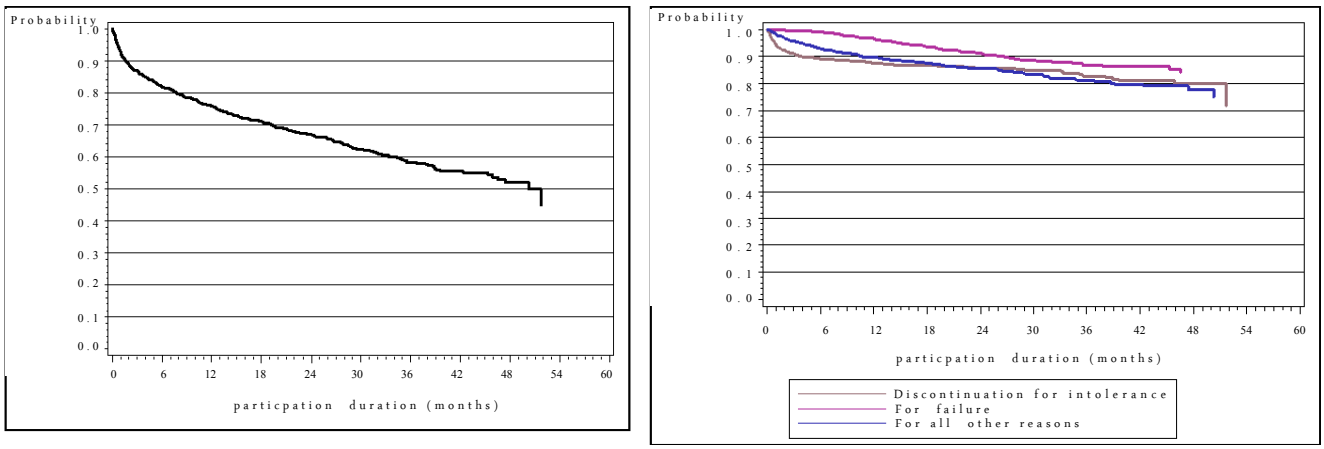

Figure 1: Time to treatment discontinuation overall (1A) and by major reason for discontinuation (1B) .

Treatment duration before discontinuation	Naïve patients (N=407)			Switch (N=696)			Failure (N=601)		
	[0-6[months (N=93)	≥ 6 months (N=55)	Total (N=148)	[0-6[months (N=93)	≥ 6 months (N=73)	Total (N=166)	[0-6[months (N=120)	≥ 6 months (N=131)	Total (N=251)
Intolerance, N (%)	47 (11.5)	9 (2.5)	56 (14)	68 (10)	22 (3)	90 (13)	65 (11)	23 (4)	88 (15)
Suspected hypersensitivity, N (%)	27 (6.6)	3 (0.7)	30 (7.3)	40 (5.7)	2 (0.3)	42 (6)	46 (7.6)	2 (0.3)	48 (7.9)
Treatment failure, N (%)	6 (2)	17 (4)	23 (6)	2 (1)	16 (2)	18 (3)	7 (1)	66 (11)	73 (12)
Other, including non adherence, N (%)	40 (10)	29 (7)	69 (17)	23 (3.3)	35 (5)	58 (8.3)	48 (8)	42 (7)	90 (15)

Table 2: Reasons for treatment discontinuation across the groups and the treatment duration.

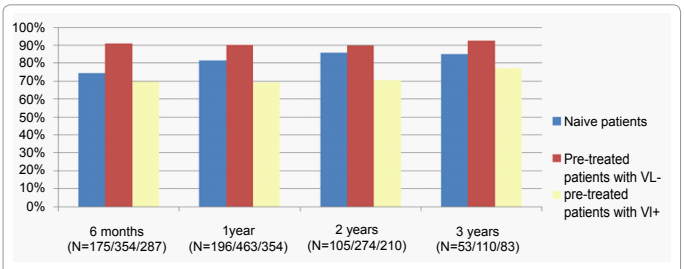

Figure 2: Proportion of patients with VL below 50 copies/mL for the naïve, switch, and failure groups, restricted to patients with available data (ITT).

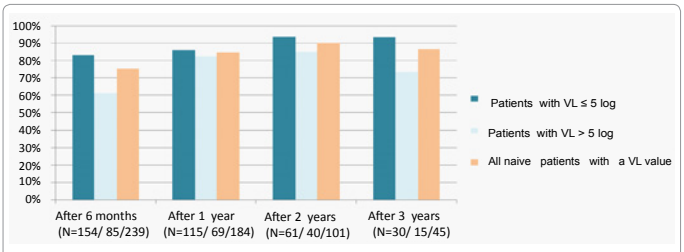

Figure 3: Proportion of patients with VL below 50 copies/mL for the naïve group, according to VL before initiation of ABC/3TC (LOCF).

a lot of clinical trials have shown with different drugs regimens in this group of patient (Figure 3).

Discussion

In this population receiving ABC/3TC before HLA-B*5701 screening was routinely available, we report that cART containing ABC/3TC in association with at least one other ARV was maintained for a median time of 52 months in the overall population. For the 565 (33%) patients in whom treatment was discontinued, the median time before discontinuation was 4 months in the patients receiving ABC/3TC as part of their first cART, 5 months in patients receiving it as a switch strategy and 7 months in those receiving it following previous virological failure. After two years, 62%, 77% and 60% of the same groups were still on ABC/3TC treatment. This duration is longer than previously described in the Swiss cohort [9] in which 45% of the patients underwent treatment discontinuation during the first year of therapy. No difference was observed when ABC/3TC was combined with either a bPI or a NNRTI in naïve or in pretreated patients, a different result was seen in ACTG5202 where a shorter "time-to-safety" event and regimen change were seen in the Efavirenz group compared to the boosted Atazanavir group but this difference could be due to the definition of safety endpoint composite of laboratory and clinical adverse events as well as the low frequency of genotype resistance testing before ABC/3TC initiation (43 to 48%) [7]. The most frequent reason for discontinuation across the population was intolerance occurring in 14% of the overall population. HSR was clinically suspected in 4% of the patients. This frequency is lower than that described in the control group of the PREDICT-1 study, defining the predictive value of HLA-B*5701 testing, were it was suspected in 7.8% of the patients. Median time to suspected HSR was longer (17 days) than described in PREDICT-1 (average time to onset of HSR symptoms of 9 days) [3]. This difference is possibly due to subjective definition of HSR and/or to data collection methods with possible memory bias if the treatment discontinuation date is retrospectively collected at the time of the next medical visit.

Discontinuation due to virological failure was infrequent as previously described in various populations of naïve or pretreated patients [10-14]. With an "on treatment" basis at two years, virological control was observed in our cohort in more than 80% of the naïve and switch patients and in around 70% of the patients with previous virological failures, comparing favorably with the results of the naïve patients of the HEAT study evaluating ABC/3TC versus tenofovir/emtricitabine (TDF/FTC) in patients receiving boosted lopinavir as third agent [15]. Cardiovascular events were as rare as previously described [16]. However, information on some risk factors were lacking such as smoking status, fasting lipid levels or measurement of blood pressure to analyze it more precisely and a more adaptive methodology including a comparison group would have been better. It is noteworthy that at the beginning of our study, cART that included a protease inhibitor was assumed to be associated with metabolic abnormalities that could increase the risk of cardiovascular disease [17,18]. ABC in association with nucleosidic reverse transcriptase inhibitors have been shown to cause a greater decrease in plasma lipid levels than did nevirapine or efavirenz [19]. These data may be responsible for a sort of channeling bias regarding ABC prescription in patients with cardio-vascular risk factors that were known to the physician but not registered in our database. Other recent studies have shown that potential confounders could exist as e.g. cocaine use or kidney disease and most analyses that control for known risk factors did not support the increased risk of MI due to ABC [5].

Finally, in this real-life large population, duration of treatment tolerability (all discontinuation causes combined) compares favorably with that reported in the randomized ACTG 5202 study comparing ABC/3TC with TDF/FTC containing regimens in antiretroviral naïve patients [7].

The observational prospective design of our study resulted in some limitations. For example, we do not collect any quantified adherence information nor up-to-date smoking habits so we are unable to provide some potentially useful information. However, long term studies including large and varied populations are difficult to carry out and yet; cohorts do provide valuable information as long as the potential biases are taken into account [20].

Conclusion

In this large cohort that is, to our knowledge, the first to report long-term use of ABC/3TC in clinical settings, we report good long term tolerability of the combination. Since HLA-B*5701 screening has been proven to significantly reduce HSR suspicion, we believe that our results may be useful. Once short term tolerance problems were resolved, long term side effects were infrequent. The use of well tolerated drugs is a mean for providing long term adherence and efficacy.

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