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Short-Term Safety and Tolerability of ABC/3TC Administered Once-daily (QD) Compared with the Separate Components Administered Twice-daily (BID): Results from ESS101822 (ALOHA)

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Background

- Highly active antiretroviral therapy (HAART) has contributed to decreased mortality and morbidity associated with HIV/AIDS^{1,2}. Non-adherence to antiretroviral medications is associated with virological failure, clinical disease progression and mortality; therefore good adherence to HAART is a critical determinant of its success³. To maximize the likelihood of success, clinicians have increasingly considered adherence and adverse events (AEs) in their treatment decisions^{4,5}. Therapy simplification, including reduced pill count, is a regimen-related strategy to improve adherence⁶.
- As a once-daily (QD) fixed dose combination, abacavir/lamivudine (ABC/3TC) has shown favorable efficacy and safety in conjunction with a variety of background therapies. The tolerability of QD dosing is mostly comparable to that of ABC and 3TC administered BID. However, at least one study noted a higher rate of hypersensitivity to abacavir (ABC HSR), including severe ABC HSR in subjects on the QD versus BID regimen⁷. The evaluation of safety endpoints, especially ABC HSR in a “real world” population is of particular interest, as the incidence of suspected HSR varies across studies.
- The aim of the Abacavir Lamivudine Once-daily HIV Assessment (ALOHA) Study was to evaluate the short-term (12-week) safety of ABC/3TC (EPZICOM™) in antiretroviral-naïve subjects, when administered as a part of an investigator-selected HAART regimen. The study duration was based on the short window of time after initiation of ABC and 3TC during which safety endpoints associated with these drugs are known to occur. In addition to safety and tolerability, adherence, patient satisfaction and efficacy endpoints were also evaluated.

Methods

Patient Selection:

This was a Phase IIIB, randomized, open-label, parallel-arm study of HIV-1-infected adults naïve to antiretroviral drugs. Patients were eligible to participate if they were naïve to antiretroviral drugs at baseline and had HIV-1 RNA >1,000 copies/mL measured within three months prior to study enrollment.

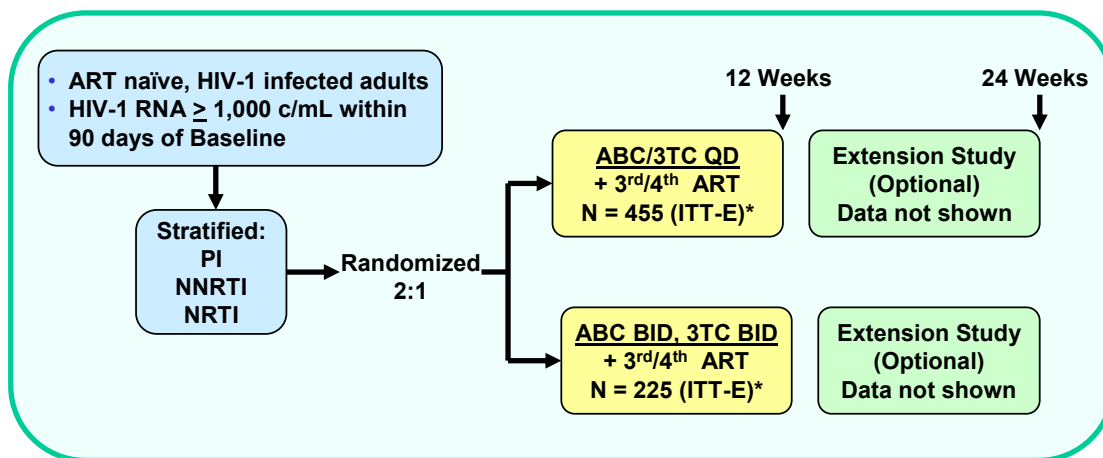
Study Design:

Multicenter study conducted at 146 sites located in the United States. Eligible subjects were randomized 2:1 to receive one of the following regimens:

- ABC 600 mg/3TC 300 mg fixed dose combination tablet (FDC) (EPZICOM™) administered QD, or
- ABC 300 mg BID (ZIAGEN®) and 3TC 150 mg BID (EPIVIR®)

Choice of third agent (or fourth agent, if appropriate) to complete a HAART regimen were at the discretion of the treating physician. Based on these choices, subjects were stratified into protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI) and nucleoside reverse transcriptase inhibitor (NRTI) groups. These agents were assigned prior to randomization, were not considered study drugs and could be substituted or dropped during the study. The study design is illustrated in Figure 1.

Figure 1. Schematic Representation of Study Design



*ITT-E comprises subjects who consumed at least one dose of the investigational products.

Assessments and Analysis:

Following randomization, subjects were given study drugs for 12 weeks, with study visits at baseline and at weeks 4, 8 and 12. Subjects then had the option of remaining on either the QD or BID arm or of switching to the QD arm for an additional 12 weeks (extension phase data not shown).

The primary endpoint of interest was short term AEs occurring within 12 weeks of initiating the regimens of interest. These included grade 2-4 AEs and all serious adverse events (SAEs). This study required that investigators report all ABC HSR events as SAEs, regardless of severity. Subjects with suspected ABC HSR were required to permanently discontinue the abacavir-containing product.

HIV-1 RNA was measured at baseline and at weeks 4, 8 and 12. CD4+ cell counts were tested at baseline and at weeks 8 and 12. Laboratory assessments were conducted locally and were therefore susceptible to variability across labs and methods used for conducting the assays.

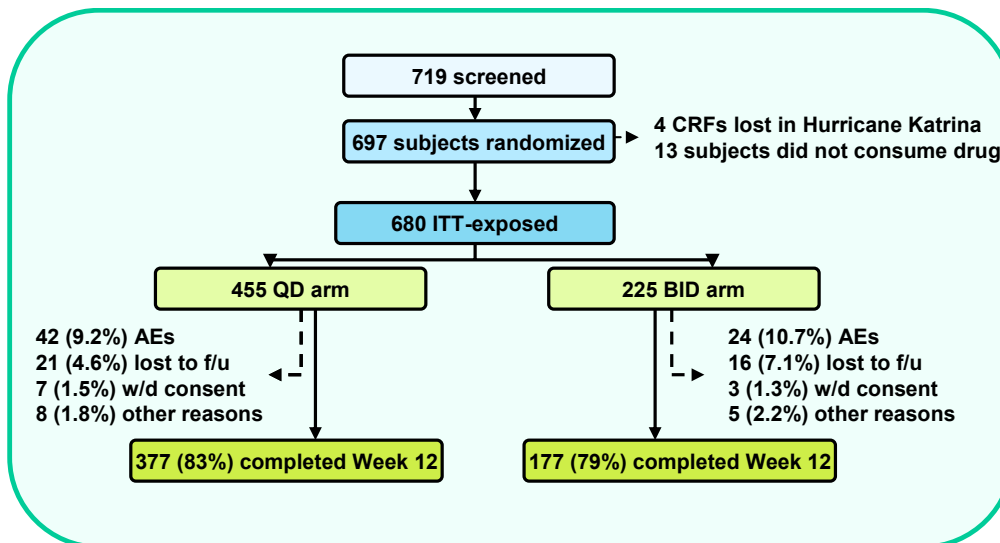
This study evaluated patient satisfaction using a validated, self-reported instrument, the status version of the HIV Treatment Satisfaction Questionnaire (HIVTSQs). The HIVTSQs was administered at week 12 or at early withdrawal. Adherence was evaluated through pill counts of study drugs at weeks 4, 8 and 12 or at early withdrawal.

All results are descriptive, consisting of generation of frequency distributions and summary statistics. Hypothesis testing was not conducted. For rates of ABC HSR, 95% confidence intervals were generated.

Results

- Among 697 subjects who were randomized to either arm of the study, 680 subjects were included in the intent-to-treat exposed (ITT-E) population, which comprised the primary analysis population. Subject disposition is illustrated in Figure 2.

Figure 2. Schematic Representation of Subject Disposition



- The distributions of demographic and clinical characteristics at baseline were similar for the two arms. Over half the subjects in this study were Black or Hispanic (Table 1). Approximately equal proportions of subjects in each arm were in the PI and NNRTI strata, with only six subjects being on a NRTI-only regimen. A larger proportion of subjects in the BID arm took nevirapine (NVP) than in the QD arm (12% and 6% respectively).

Table 1. Summary of Demographic and Clinical Characteristics at Baseline

Parameter	ABC/3TC QD (n=455)	ABC+3TC BID (n=225)
Age: Median (range)	40 (19, 75)	38 (20, 73)
Male %	82%	86%
White, Black, Hispanic (%)	44, 37, 17%	47, 30, 20%
CDC Class A, B, C (%)	65, 14, 22%	72, 13, 15%
Median log ₁₀ HIV-1 RNA (range)	4.9 (1.7 – 6.7)	4.9 (1.6 – 6.0)
Median CD4+ (range)	222 (1 – 1168)	228 (0 – 995)
Strata^{†‡}		
NNRTI, n (%)	233 (51%)	116 (52%)
Efavirenz	210 (46%)	99 (44%)
Nevirapine	27 (6%)	27 (12%)
PI, n (%)	232 (51%)	111 (50%)
Atazanavir	68 (15%)	23 (10%)
Atazanavir-Ritonavir	47 (10%)	27 (12%)
Lopinavir-Ritonavir	47 (10%)	25 (11%)
Fosamprenavir-Ritonavir	40 (9%)	12 (5%)
Fosamprenavir	18 (4%)	16 (7%)

[†]Only 4 subjects in the BID arm and 2 subjects in the QD arm were on an NRTI-only regimen and are not presented in the above table.

[‡]The number of subjects in individual drugs do not add up to 100% since this study allowed inter-and intra-class switching

Overall, the EPZICOM™ QD and ZIAGEN® BID arms were well-tolerated with a low incidence of AEs over 12 weeks of follow-up (Table 2).

Table 2. Summary of Grade 2-4 Adverse Events and Serious Adverse Events

	ABC/3TC QD n = 455	ABC+3TC BID n = 225
Overall results		
All Grade 2-4 AEs	150 (33%)	69 (31%)
Drug-related Grade 2-4 AEs	47 (10%)	36 (16%)
All SAEs	49 (11%)	22 (10%)
Drug-related SAEs	21 (5%)	17 (8%)
Stratified results[†]		
NNRTI	N=233	N=116
All Grade 2-4 AEs	75 (32%)	36 (31%)
Drug-related Grade 2-4 AEs	21 (9%)	20 (17%)
All SAEs	21 (9%)	11 (9%)
Drug-related SAEs	10 (4%)	10 (9%)
PI	N=218	N=107
All Grade 2-4 AEs	75 (34%)	33 (31%)
Drug-related Grade 2-4 AEs	26 (12%)	16 (15%)
All SAEs	28 (13%)	11 (10%)
Drug-related SAEs	11 (5%)	7 (7%)

[†]Results for the NRTI stratum are not shown because of small sample size.

- There were 36 suspected ABC HSR events in this study (Table 3), with the rates being 4.4% and 7.1% in the QD and BID arms respectively. All ABC HSR events were termed SAEs by study convention. However, only 4 events in the QD arm (0.9%) and 5 events in the BID arm (2.2%) were considered to be grade 3-4. Subjects in the NNRTI stratum of the BID arm were most likely to experience suspected ABC HSR (Figure 3). One death in the BID arm was considered to be possibly related to rechallenge ABC HSR. This subject reportedly re-started ABC upon improvement of the symptoms following initial exposure, despite being instructed by a physician to permanently discontinue the product. However it was not known whether or not the patient actually restarted ABC, or any other component of his study regimen. The final diagnoses for this subject included bilateral pneumonitis, respiratory failure requiring ventilator support, severe hypoxia secondary to adult respiratory distress syndrome (ARDS) and sepsis syndrome, and rechallenge reaction to ABC could not be ruled out.

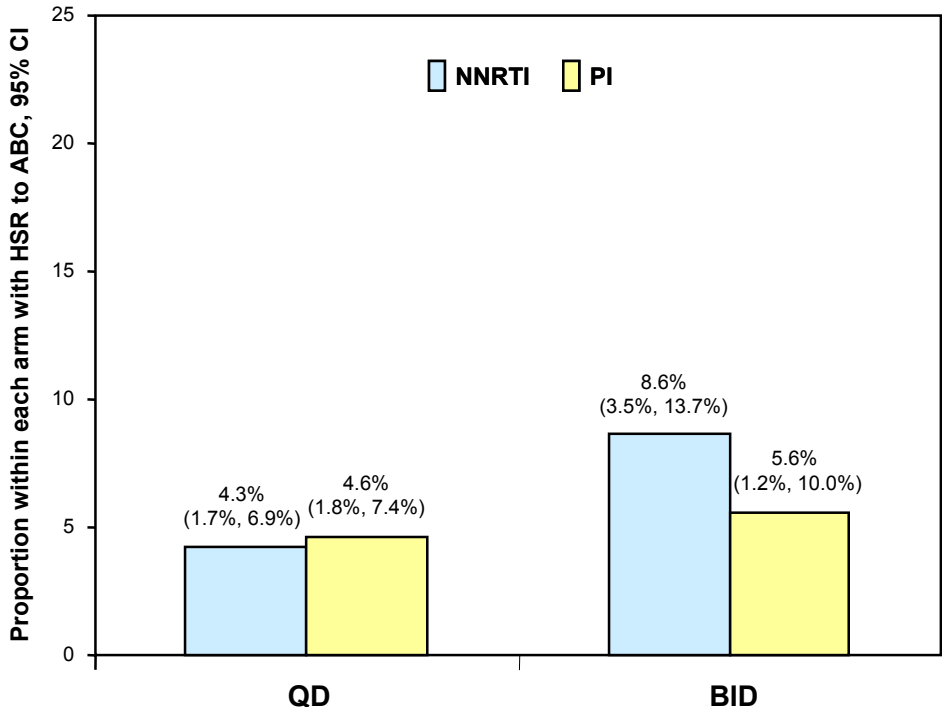
Table 3. Summary of Suspected Abacavir Hypersensitivity Events

	ABC/3TC QD n = 455	ABC+3TC BID n = 225
Overall results		
Suspected ABC HSR events	20 (4.4%)	16 (7.1%)
95% CI	[2.5%, 6.3%]	[3.8%, 10.5%]
HSR severity Grade 3-4	4 (0.9%)	5 (2.2%)
HSR associated with death	0 (0%)	1 (0.4%)
HSR associated with hospitalization	3 (0.7%)	1 (0.4%)
Stratified results[*]		
NNRTI	n=233	n=116
Suspected ABC HSR events	10 (4.3%)	10 (8.6%)
95% CI	[1.7%, 6.9%]	[3.5%, 13.7%]
PI	n=218	n=107
Suspected ABC HSR events	10 (4.6%)	6 (5.6%)
95% CI	[1.8%, 7.4%]	[1.2%, 10%]

^{*}Results for the NRTI stratum have not been shown because of small sample size.

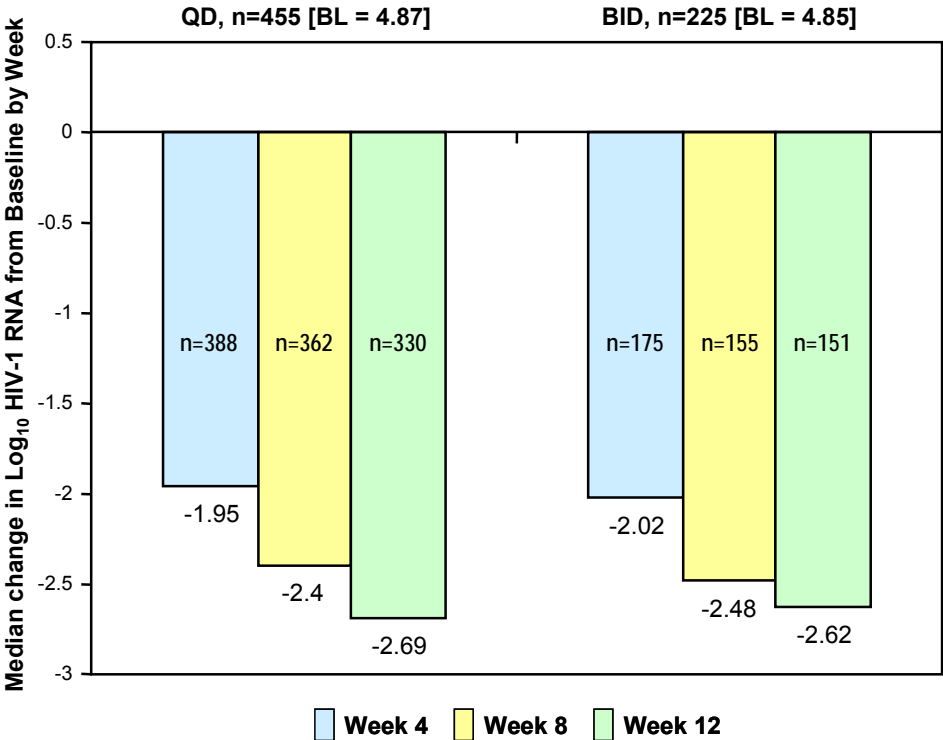
NOTE: All suspected ABC HSR events were classified as serious adverse events (SAEs) regardless of the severity as defined by ICH guidelines.

Figure 3. Summary of Suspected Abacavir Hypersensitivity Events by Study Strata



- As indicated in Figure 4, at week 12, subjects experienced a -2.69 and -2.62 median change from baseline in \log_{10} HIV-1 RNA. The median change in CD4+ cells from baseline to week 12 was +108 and +124 cells/mm³ in the QD and BID arms respectively.

Figure 4. Median change in HIV-1 RNA from Baseline by Week of Assessment



- Median adherence to study drugs over 12 weeks was similar across the study arms (QD: 94.3%, BID: 92.9%). The total mean patient satisfaction scores were also similar between groups (QD: 91.7, BID 88.7) (Table 4).

Table 4. Summary of Adherence and Treatment Satisfaction Data

Summary of Adherence Rates		
	ABC/3TC QD	ABC+3TC BID
Overall Median Adherence	94% (5-100%) n = 411	93% (6-100%) n = 195
NNRTI	94% (7-100%) n = 210	93% (6-100%) n = 105
PI	94% (5-100%) n = 197	93% (26-100%) n = 89
Summary of HIVTSQs Score		
	ABC/3TC QD	ABC+3TC BID
Overall Mean ± SD	92 ± 13 n = 364	89 ± 14 n = 183
NNRTI	93 ± 11 n = 185	89 ± 14 n = 98
PI	90 ± 14 n = 175	88 ± 14 n = 84

NOTE: Results for the NRTI stratum are not presented because of small sample size.
Adherence = Number of pills actually taken ÷ Number of pills prescribed

Discussion

- The AE profiles were similar between the QD arm and the BID arm of the study, although a lower percentage of subjects in the QD arm experienced drug-related grade 2-4 AEs than in the BID arm.
- About half the subjects in this study were on NNRTIs and nearly a third of all subjects were on boosted PI-regimens. A larger percentage of events was observed in the NNRTI stratum of the BID arm than in any other stratum.
 - Of note, a larger proportion of subjects in the BID arm were on NVP than in the QD arm (12% and 6% respectively). However, this study was not powered to formally compare treatment arms, so statistical comparisons were not conducted.
- The rate of suspected ABC HSR was slightly lower in the QD (4.4%) versus BID (7.1%) arm, as were the percentages of severe events (<1% and 2.2% for QD and BID respectively) which were found to be higher among subjects on the QD regimen in CNA30021 (4.9%).

Conclusion

- **This study demonstrated the short-term safety and tolerability of ABC and 3TC taken once daily with a wide range of background medications in real-world clinic settings.**
- **AE and SAE rates do not appear to be different across the two arms of the study. The observed rates of ABC HSR are consistent with the label. The data do not suggest that event rate in the QD arm is higher than that in the BID arm.**
- **The treatment arms appear to be similar in terms of median change in HIV-1 RNA and CD4+ cells from baseline.**

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