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Long-Term Safety and Tolerability of the Lamivudine/Abacavir Combination as Components of Highly Active Antiretroviral Therapy

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Abstract

Background: Numerous large, long-term clinical trials have assessed the safety and efficacy of the two antiretroviral nucleoside analogs lamivudine and abacavir as components of highly active antiretroviral therapy for the treatment of patients with HIV-1 infection. This analysis pools the safety data on multi-drug regimens containing lamivudine/abacavir in combination with a protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or nucleoside reverse transcriptase inhibitor.

Methods: Data are presented from 2279 treatment-naive HIV-1-infected patients who were enrolled in one of five clinical trials that assessed the safety and tolerability of lamivudine/abacavir in combination with a third antiretroviral agent. The well characterised combination of lamivudine/zidovudine plus efavirenz was used as the comparator arm. All available safety data (including data beyond 48 weeks) were used in all analyses, which included calculation of treatment emergent laboratory values, adverse events (AEs), serious AEs, fatalities, drug discontinuations and any summaries by study week of safety data.

Results: In the total lamivudine/abacavir group, 1585 of 2229 (71%) patients experienced at least one drug-related AE during the study compared with 247 of 325 (76%) patients in the lamivudine/zidovudine/efavirenz treatment group. The most common drug-related AEs reported during the study were diarrhoea (19%), nausea (18%) and dizziness (12%) in patients treated with lamivudine/abacavir plus a third agent, and nausea (31%), dizziness (27%) and headache (16%) in the comparator group. Overall, in the total lamivudine/abacavir group there were only three severe (Division of AIDS 1992 toxicity table grade 3 or 4) AEs that were reported in >1% of subjects: drug hypersensitivity, elevated ALT levels and elevated AST levels. In the lamivudine/zidovudine/efavirenz group, six severe AEs that occurred in >1% of the safety population were reported. The abacavir hypersensitivity reaction rate reported in these five studies was comparable with

the previously reported rate. In addition, there were no patient fatalities attributed by investigators to the study drugs.
Conclusion: This analysis indicates that the combination of lamivudine/abacavir is generally safe for the majority of patients when used as part of combination therapy.

Background

Since the introduction of multi-drug, highly active antiretroviral therapy (HAART) for the treatment of HIV-1 disease in 1995, both the length and quality of life for HIV-infected individuals has been notably expanded.[1-8] As eradication of HIV/AIDS is not feasible with currently approved therapies, the course of delaying disease progression and preventing opportunistic infections is best achieved by well tolerated, compact drug regimens with acceptable short- and long-term safety profiles. These regimen characteristics combined with high rates of medication adherence and tolerability are recognised as critical predictors of longer term viral suppression.[9,10] Likewise, poor adherence and/or tolerability have been associated with an increased likelihood of virological failure, the development of drug resistance and increased morbidity and mortality.[11-14]

Long-term data from large trials of the combination of two currently approved antiretroviral nucleoside analogs lamivudine and abacavir have confirmed their utility as components of HAART, with excellent virological suppression in the long-term treatment of HIV-1 infection.[15-20] Lamivudine and abacavir have been used in a number of clinical studies over the past 7 years, both alone and in combination, as the primary nucleoside reverse transcriptase inhibitor (NRTI) backbone of HAART for the treatment of both naive and antiretroviral therapy (ART)-experienced patients with HIV-1.[21-23] Many of these clinical studies have evaluated the antiviral efficacy, safety and tolerability of lamivudine (300mg total daily dose) plus abacavir (600mg total daily dose) as components of a multi-drug (≥3 drugs) antiretroviral combination therapy.[24-28]

In this analysis, study safety data are examined from treatment naive, HIV-1-infected adult patients in order to analyse the safety and tolerability of lamivudine/abacavir in combination with a protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or NRTI, over a minimum of 48 weeks of HAART. However, it should be noted that these five studies do not represent the totality of clinical trials that have used this nucleoside backbone, but rather reflect the most recent and well controlled clinical data that refine our current understanding of the safety profiles of these antiretroviral combinations.[29-35]

Methods

This lamivudine/abacavir safety analysis has drawn data from the safety populations of each of the following GlaxoSmithKline-sponsored studies: CNA30021,[17] CNA30024,[16] ESS40001,[19] APV30001[15] and APV30002[18] (table I). These trials grouped ART-naive patients into six distinct treatment groups based on the third agent in the three-drug regimen. Although each of these studies has been reported individually in separate scientific publications, this analysis will concentrate primarily on the safety and tolerability of the lamivudine/abacavir combination compared with the single comparator arm of the well characterised combination of lamivudine plus zidovudine.[15-20] The agents used in combination with lamivudine/abacavir were

Table I. Summary of clinical trials included in this analysis

Study Identifier	Study design	Total no. of patients enrolled (patients in each arm)	Drug regimen (mg)		
			arm 1	arm 2	arm 3
CNA30021 (ZODIAC)[17]	r, db, c	770 (384/386)	3TC 300 od ABC 600 od EFV 600 od	3TC 300 od ABC 300 bid EFV 600 od	NA
CNA30024[16]	r, db, c	649 (324/325)	3TC 150 bid ABC 300 bid EFV 600 od	3TC 150 bid ZDV 300 bid EFV 600 od	NA
ESS40001 (CLASS)[19]	r, op, c	291 (97/96/98)	3TC 150 bid ABC 300 bid EFV 600 od	3TC 150 bid ABC 300 bid APV *or* FPV 1400 od RTV 200 od	3TC 150 bid ABC 300 bid d4T 30 *or* 40 bid
APV30001 (NEAT)[15]	r, op, c	249 (166/83)	3TC 150 bid ABC 300 bid FPV 1400 bid	3TC 150 bid ABC 300 bid NFV 1250 bid	NA
APV30002 (SOLO)[18]	r, op, c	649 (322/327)	3TC 150 bid ABC 300 bid FPV 1400 od RTV 200 od	3TC 150 bid ABC 300 bid NFV 1250 bid	NA

3TC = lamivudine; **ABC** = abacavir; **APV** = amprenavir; **bid** = twice a day; **c** = controlled; **d4T** = stavudine; **db** = double blind; **EFV** = efavirenz; **FPV** = fosamprenavir; **NFV** = nelfinavir; **od** = once daily; **op** = open label; **r** = randomised; **RTV** = ritonavir; **ZDV** = zidovudine.

efavirenz, nelfinavir, fosamprenavir or amprenavir, fosamprenavir/ritonavir and stavudine.

The safety population in this analysis included patients enrolled in the CNA30021,[17] CNA30024,[16] ESS40001,[19] APV30001[15] or APV30002[18] studies who were exposed to study medications. Analyses were performed for all patients who received at least one dose of lamivudine/abacavir or lamivudine/zidovudine study medications as part of combination therapy. All available safety data were included in all analyses of the data, which included calculation of treatment emergent laboratory values, adverse events (AEs), serious adverse events (SAEs), and any summaries by study week of safety data. The duration of therapy (48 weeks) was established *a priori* based on drug approval guidelines at the time the studies were conducted. The five studies continued until the last patient had completed 48 weeks of therapy, so actual follow-up exceeded 48 weeks.

Safety-population data were included for analysis if the patient met all of the following criteria:

- Participated in one of the following registrational clinical trials: CNA30021,[17] CNA30024,[16] ESS40001,[19] APV30001[15] or APV30002.[18]
- Confirmed to be an HIV-1-infected, treatment-naive adult receiving a three-drug ART regimen.
- Had been randomised to receive a study regimen of two NRTIs plus PI or NNRTI or NRTI.

Safety-population data were excluded from analysis if the patient met one of the following criteria:

- Did not take study drug(s).
- Patient's safety data were not collected while receiving study drug(s).

During the conduct of each study, safety data were captured for each study patient separately. Patients in all five studies were asked at each study visit, in a non-leading manner, about any medical complaints they had since the last study visit. AE details such as event start and stop dates, severity, causality, seriousness, outcome and action taken with study regimens were documented by study site personnel for each separate study patient. The severity of AEs was graded according to the Division of

AIDS 1992 toxicity table[36] or, if not listed on the toxicity table, coded as 'mild', 'moderate' or 'severe' based on the investigators' clinical judgement. In addition, investigators were required to assign causality of AEs to a study regimen because the AE data were collected on the entire study regimen, investigators rarely specified if an AE was considered related to an individual study drug. For this reason, events referred to as 'drug-related' were those considered by the study investigators to be related to the study regimen.

All AEs within this safety analysis were added to a database and coded or re-coded using Medical Dictionary for Regulatory Activities (MedDRA) terms as outlined in the Maintenance and Support Services Organization website.[37] For this reason, prior study information and presentations for the ESS40001[19] and CNA30024[16] studies, reported using the Medical Information and Documentation Automated System (MIDAS) terms, may not be reflective of the previously reported incidences within this manuscript.

AEs were tabulated by treatment group, maximum intensity, seriousness and attributability as assessed by investigators or qualified study site personnel. All AEs, treatment-emergent AEs (laboratory and clinical AEs), severe/Division of AIDS 1992 toxicity table grades 3 or 4 AEs, AEs leading to discontinuation and SAEs were summarised for the various treatment groups.

Across all the studies, an AE was defined as any untoward medical occurrence in a patient adminis-

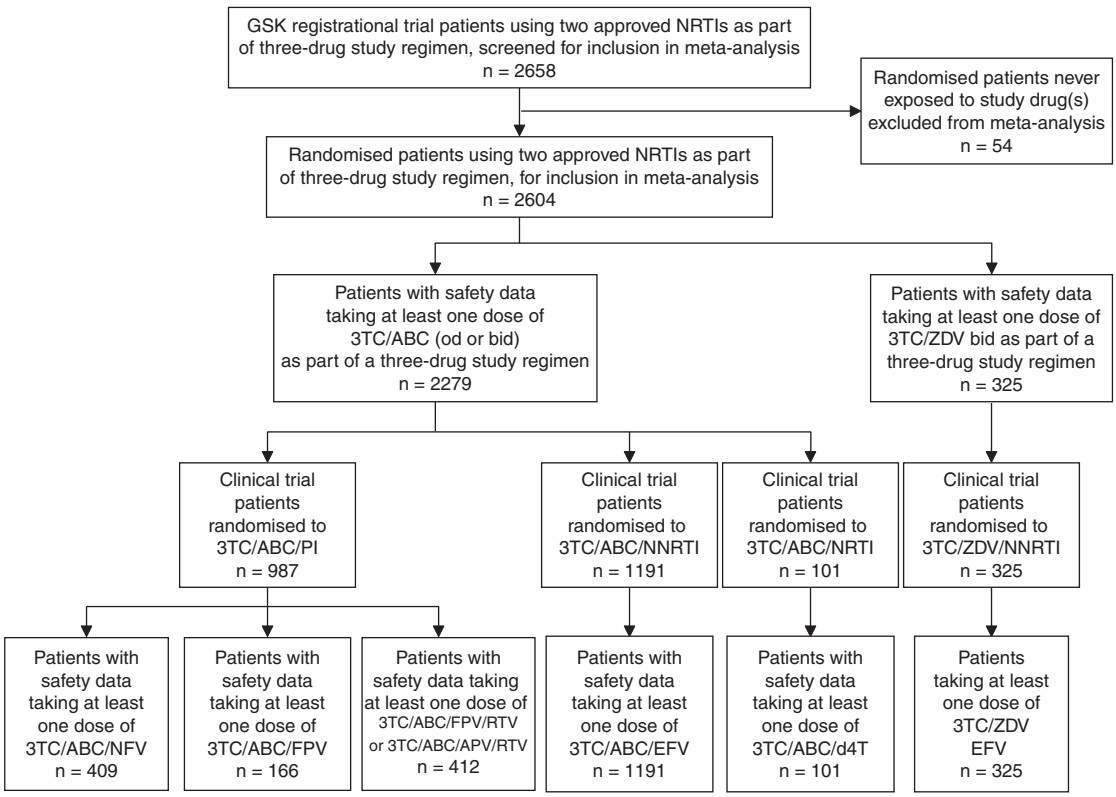

Fig. 1. Data-extraction flow diagram. **3TC** = lamivudine; **ABC** = abacavir; **APV** = amprenavir; **bid** = twice a day; **d4T** = stavudine; **EFV** = efavirenz; **FPV** = fosamprenavir; **GSK** = GlaxoSmithKline; **NFV** = nelfinavir; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside reverse transcriptase inhibitor; **od** = once a day; **PI** = protease inhibitor; **RTV** = ritonavir; **ZDV** = zidovudine.

Table II. Key baseline and demographic characteristics of the five lamivudine/abacavir (3TC/ABC) treatment groups and the control group

Characteristics	+ EFV n = 1191	+ NFV n = 409	+ FPV n = 166	+ RTV and FPV or APV n = 412	+ d4T n = 101	Control[a] n = 325
Age in years, median (min, max)	36 (18, 74)	36 (18, 68)	36 (17, 70)	36 (18, 69)	34 (20, 72)	35 (20, 74)
Sex [n (%)]						
male	965 (81)	306 (75)	115 (69)	306 (74)	84 (83)	267 (82)
female	226 (19)	103 (25)	51 (31)	106 (26)	17 (17)	58 (18)
Race [n (%)]						
White	607 (51)	195 (48)	42 (25)	184 (45)	32 (32)	167 (51)
Black	310 (26)	135 (33)	52 (31)	149 (36)	29 (29)	70 (22)
American Hispanic	238 (20)	63 (15)	71 (43)	62 (15)	37 (37)	80 (25)
Asian	20 (2)	7 (2)	1 (<1)	7 (2)	1 (<1)	2 (<1)
other	16 (1)	9 (2)	0	10 (2)	2 (2)	6 (2)
Baseline values [median (range)]						
HIV-1 RNA PCR (log_{10} copies/mL)	4.87	4.83	4.81	4.82	4.82	4.76
CD4+ cell count (cells/mm^3)	265	182	214	188	277	258
CDC Classification of HIV [n (%)]						
Class A – asymptomatic	905 (76)	226 (55)	103 (62)	239 (58)	80 (79)	249 (77)
Class B – symptomatic, not AIDS	211 (18)	94 (23)	30(18)	96 (23)	14 (14)	58 (18)
Class C – AIDS	74 (6)	89 (22)	33 (20)	76 (18)	7 (7)	18 (6)
Unknown	1 (<1)	0	0	1 (<1)	0	0

a 3TC/ZDV/EFV.

APV = amprenavir; **CDC** = Centers for Disease Control (US); **d4T** = stavudine; **EFV** = efavirenz; **FPV** = fosamprenavir; **NFV** = nelfinavir; **PCR** = polymerase chain reaction; **RTV** = ritonavir; **ZDV** = zidovudine.

tered a drug product or regimen, which did not necessarily have a causal relationship with the drug product or regimen. An AE could therefore be any unfavourable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom or disease temporally associated with the use of the drug product whether or not considered related to the actual product.

An SAE was any AE that occurred at any dose that resulted in death, a life-threatening event, hospitalisation, occurrence of a congenital anomaly or a medical event that in the opinion of the investigator may have resulted in one of the former events. For tracking purposes, all cases of abacavir hypersensitivity reaction were reported as SAEs regardless of whether the event met this definition of serious or of the severity of the event.

Results

Patient Data

Data were available for a total of 2279 patients subdivided into treatment groups based on the NRTI nucleoside backbone and third antiretroviral agent of the antiretroviral regimen as follows: lamivudine/abacavir/efavirenz (n = 1191); lamivudine/abacavir/nelfinavir (n = 409); lamivudine/abacavir/fosamprenavir or lamivudine/abacavir/amprenavir (n = 166); lamivudine/abacavir/fosamprenavir/ritonavir (n = 412); and lamivudine/abacavir/stavudine (n = 101). The single treatment group of lamivudine/zidovudine/efavirenz (n = 325) from the CNA30024[16] study was used as the comparator arm within this analysis. The extraction of the lamivudine/abacavir safety data into discreet treatment groups allowed for the evaluation of the safety

profile of the lamivudine/abacavir combination as a component of triple drug therapy with NRTIs, NNRTIs or PIs across large, diverse study populations (see figure 1).

Baseline Demographics

Key baseline patient demographics and disease characteristics for the safety populations are summarised in table II and were comparable among the multiple treatment groups. Median baseline plasma HIV-1 RNA polymerase chain reaction values ranged from 4.81 to 4.87 $\log_{10}$ copies/mL in the five lamivudine/abacavir treatment groups compared with 4.76 $\log_{10}$ copies/mL in the lamivudine/zidovudine/efavirenz group. However, the CD4+ cell counts and US Centers for Disease Control (CDC) classification of HIV-1 disease were variable across studies as a result of the differing target populations of the five clinical studies.

Treatment Discontinuation Rates

The percentage of patients completing ≥48 weeks of treatment was similar across the various lamivudine/abacavir treatment groups (table III). A total of 2279 adult patients were randomised to receive lamivudine/abacavir in combination with a third agent compared with 325 patients who were randomised to receive lamivudine/zidovudine/efavirenz. Overall, 75% of patients (1719/2279) completed ≥48 weeks of study treatment with lamivudine/abacavir versus 77% of patients (250/325) in the lamivudine/zidovudine/efavirenz treatment group, which was not statistically different.

Any patient not completing 48 weeks of treatment was categorised as prematurely discontinuing the study regimen. Reasons for premature discontinuation of lamivudine/abacavir were comparable across treatment groups with an overall 25% (560/2279) of patients discontinuing treatment prior to completion of the study versus 23% (75/325) observed in the lamivudine/zidovudine/efavirenz treatment group. The combined lamivudine/abacavir group had a lower percentage of discontinuations due to AEs or lost to follow-up than the lamivudine/zidovudine/efavirenz group; however, these differences were not statistically different. In contrast, the incidence of discontinuation due to insufficient viral load response was 3-fold higher in the total lamivudine/abacavir group (9%) than the lamivudine/zidovudine/efavirenz group (3%).

Table III. Patient disposition for the five lamivudine/abacavir (3TC/ABC) treatment groups

Patient disposition	+ EFV n = 1191	+ NFV n = 409	+ FPV n = 166	+ RTV and FPV or APV	+ d4T n = 101	Total 3TC/ABC n = 2279	Control[a] n = 325
Treated population [n (%)]							
Completed 48 weeks on study	912 (77)	307 (75)	116 (70)	299 (73)	85 (84)	1719 (75)	250 (77)
Discontinued study	279 (23)	102 (25)	50 (30)	113 (27)	16 (16)	560 (25)	75 (23)
Primary reason for discontinuation[n (%)]							
Adverse event	66 (24)	22 (22)	9 (18)	31 (27)	2 (13)	130 (23)	25 (33)
Consent withdrawn	39 (14)	14 (14)	6 (12)	23 (20)	5 (31)	87 (15)	6 (8)
Lost to follow-up	104 (37)	23 (23)	18 (36)	35 (31)	7 (44)	187 (33)	34 (45)
Clinical progression	5 (2)	1 (<1)	1 (2)	0	0	7 (1)	1 (1)
Protocol violation	9 (3)	4 (4)	0	5 (4)	1 (6)	19 (3)	0
Insufficient viral load response	13 (5)	24 (24)	11 (22)	1 (<1)	0	49 (9)	2 (3)
Other	43 (15)	14 (14)	5 (10)	18 (16)	1 (6)	81 (14)	7 (9)

a 3TC/ZDV/EFV.

APV = amprenavir; **d4T** = stavudine; **EFV** = efavirenz; **FPV** = fosamprenavir; **NFV** = nelfinavir; **RTV** = ritonavir; **ZDV** = zidovudine.

Table IV. Number (percentage) of most commonly reported adverse events with lamivudine/abacavir (3TC/ABC)[a]

Adverse events	+ EFV n = 1191	+ NFV n = 409	+ FPV n = 166	+ RTV and FPV or APV n = 412	+ d4T n = 101	Total 3TC/ABC n = 2279	Control[b] n = 325
Patients with any event	1119 (94)	396 (97)	158 (95)	387 (94)	95 (94)	2155 (95)	307 (94)
Diarrhoea	217 (18)	231 (56)	47 (28)	167 (41)	26 (26)	688 (30)	58 (18)
Nausea	265 (22)	111 (27)	65 (39)	150 (36)	30 (30)	621 (27)	121 (37)
Headache	213 (18)	99 (24)	31 (19)	85 (21)	20 (20)	448 (20)	80 (25)
Dizziness	273 (23)	28 (7)	7 (4)	34 (8)	11 (11)	353 (15)	99 (30)
Fatigue	188 (16)	54 (13)	17 (10)	63 (15)	21 (21)	343 (15)	72 (22)
Rash	188 (16)	56 (14)	41 (25)	40 (10)	15 (15)	340 (15)	55 (17)
Insomnia	220 (18)	41 (10)	17 (10)	31 (8)	12 (12)	321 (14)	51 (16)
Upper respiratory infection	127 (11)	68 (17)	26 (16)	77 (19)	17 (17)	315 (14)	30 (9)
Vomiting	114 (10)	59 (14)	27 (16)	79 (19)	18 (18)	297 (13)	67 (21)
Nasopharyngitis	174 (15)	37 (9)	18 (11)	40 (10)	22 (22)	291 (13)	49 (15)
Depression	138 (12)	30 (7)	12 (7)	26 (6)	19 (19)	225 (10)	31 (10)
Abnormal dreams	177 (15)	3 (<1)	1 (<1)	2 (<1)	2 (2)	185 (8)	40 (12)

a The numbers of adverse events may exceed the total number of patients because some patients reported more than one event.

b 3TC/ZDV/EFV.

APV = amprenavir; **d4T** = stavudine; **EFV** = efavirenz; **FPV** = fosamprenavir; **NFV =** nelfinavir; **RTV** = ritonavir; **ZDV** = zidovudine.

Summary of Adverse Events (AEs)

The majority of the patients in each treatment group experienced at least one AE during their participation in a clinical study: lamivudine/abacavir plus a third agent (efavirenz 94%; nelfinavir 97%; fosamprenavir 95%; fosamprenavir [or amprenavir]/ritonavir 94%; stavudine 94%) or lamivudine/zidovudine/efavirenz (94%). The most common AEs reported by treatment group are summarised in table IV. The combination of lamivudine/abacavir with a PI, NRTI, or NNRTI in treatment naive patients had similar incidences of AEs reported as the comparator arm, lamivudine/zidovudine/efavirenz.

Summary of Drug-Related AEs

In the total lamivudine/abacavir group, 1585 of 2229 (71%) patients experienced at least one drug-related AE during the study compared with 247 of 325 (76%; p = 0.012 Fisher's exact test) patients in the lamivudine/zidovudine/efavirenz treatment group. The most common drug-related AEs reported by patients across the treatment groups are summarised in table V. Incidences of drug-related AEs were generally comparable and of low occurrence between the various treatment groups with the exception of dizziness, which was significantly (2-fold) higher in the lamivudine/zidovudine/efavirenz group than all other groups. When comparing the reported drug-related AEs between the lamivudine/abacavir/efavirenz group and the lamivudine/zidovudine/efavirenz group, the rate was statistically significantly higher in the latter (p = 0.02).

Summary of Severe (Grades 3 and 4) AEs

All reported severe (grade 3 and 4) AEs are summarised in table VI. Though infrequent, the reported severe events listed in table VI have been observed in prior clinical studies using lamivudine/abacavir. Overall, in the total lamivudine/abacavir group there were only three severe AEs that were reported in >1% of subjects: drug hypersensitivity, elevated ALT levels and elevated AST levels. In the lamivudine/zidovudine/efavirenz group, six severe AEs that occurred in >1% of the safety population

were reported. Of note, the incidence of severe diarrhoea occurred in only 1% of all patients in these trials and did not differ to the incidence reported in the lamivudine/zidovudine/efavirenz comparator group.

Summary of Serious AEs

Incidences of SAEs were generally comparable across treatment groups, with 416 of 2279 (18%) of subjects in the lamivudine/abacavir treatment groups experiencing an SAE compared with 46 of 325 (14%) of patients in the lamivudine/zidovudine/efavirenz group. All reported SAEs are summarised in table VII. The only SAE reported that occurred in >1% of patients was drug hypersensitivity. There were no apparent trends in reported SAEs with most other SAEs occurring in <1% of patients in any treatment group regardless of nucleoside backbone or third agent. All cases of suspected abacavir hypersensitivity reaction were classified as SAEs, regardless of severity or whether the cases met the regulatory definition of seriousness.

Summary of Fatalities

There were 23 of 2604 (<1%) reported patient fatalities that occurred during the conduct of these five clinical trials. All details of reported fatalities are summarised in table VIII. In some cases, multiple clinical AEs were reported for a single patient that resulted in a fatal outcome. None of the fatalities were considered by the investigator to be attributable to lamivudine/abacavir or the other drugs under study, and all were assigned to the natural progression of disease or prior health condition. No fatalities were reported in the lamivudine/abacavir/fosamprenavir or lamivudine/abacavir/stavudine treatment groups. There were no trends observed in patients that had a fatal event while taking lamivudine/abacavir and any third antiretroviral agent or lamivudine/zidovudine/efavirenz.

Table V. Number (percentage) of most common drug-related adverse events with lamivudine/abacavir (3TC/ABC)[a]

Drug-related adverse event	+ EFV n = 1191	+ NFV n = 409	+ FPV n = 166	+ RTV and FPV or APV n = 412	+ d4T n = 101	Total 3TC/ABC n = 2279	Control[b] n = 325
Patients with any event	840 (71)	298 (73)	101 (61)	294 (71)	52 (51)	1585 (70)	247 (76)
Nausea	183 (15)	87 (21)	53 (32)	122 (30)	18 (18)	413 (18)	101 (31)
Diarrhoea	93 (8)	191 (47)	29 (17)	118 (29)	11 (11)	442 (19)	27 (8)
Dizziness	227 (19)	14 (3)	4 (2)	18 (4)	3 (3)	266 (12)	87 (27)
Headache	92 (8)	37 (9)	13 (8)	37 (9)	5 (5)	184 (8)	53 (16)
Fatigue	106 (9)	21 (5)	8 (5)	38 (9)	9 (9)	182 (8)	46 (14)
Insomnia	150 (13)	14 (3)	7 (4)	8 (2)	1 (<1)	180 (8)	38 (12)
Drug hypersensitivity	84 (7)	30 (7)	16 (10)	33 (8)	7 (7)	175 (8)	10 (3)[c]
Vomiting	56 (5)	35 (9)	20 (12)	57 (14)	6 (6)	174 (8)	39 (12)
Abnormal dreams	167 (14)	3 (<1)	1 (<1)	0	1 (<1)	172 (8)	38 (12)
Rash	99 (8)	24 (6)	20 (12)	14 (3)	4 (4)	161 (7)	37 (11)
Loose stools	17 (1)	46 (11)	5 (3)	31 (8)	1 (<1)	100 (4)	5 (2)
Abdominal pain	31 (3)	21 (5)	7 (4)	19 (5)	1 (<1)	79 (3)	9 (3)
Somnolence	59 (5)	1 (<1)	2 (1)	3 (<1)	1 (<1)	66 (3)	21 (6)

a The numbers of adverse events may exceed the total number of patients because some patients reported more than one event.

b 3TC/ZDV/EFV.

c During the blinded portion of the study, investigators reported 3% incidence of suspected ABC hypersensitivity reaction in the ZDV/3TC/EFV arm.

APV = amprenavir; **d4T**= stavudine; **EFV** = efavirenz; **FPV** = fosamprenavir; **NFV** = nelfinavir; **RTV** = ritonavir; **ZDV** = zidovudine.

Table VI. Number (percentage) of all severe (grades 3 and 4) adverse events reported with lamivudine/abacavir (3TC/ABC)

Severe adverse event	+ EFV n = 1191	+ NFV n = 409	+ FPV n = 166	+ RTV and FPV or APV n = 412	+ d4T n = 101	Total 3TC/ABC n = 2279	Control[a] n = 325
Patients with any event	300 (25)	105 (26)	26 (16)	125 (30)	36 (36)	592 (26)	92 (28)
Drug hypersensitivity	33 (3)	11 (3)	5 (3)	10 (2)	3 (3)	62 (3)	0
Increased ALT level	20 (2)	15 (4)	5 (3)	14 (3)	3 (3)	57 (3)	7 (2)
Increased AST level	21 (2)	11 (3)	3 (2)	12 (3)	2 (2)	49 (2)	4 (1)
Depression	17 (1)	5 (1)	1 (<1)	6 (1)	3 (3)	32 (1)	3 (<1)
Hypertriglyceridemia	17 (1)	3 (<1)	0	5 (1)	5 (5)	30 (1)	3 (<1)
Neutropenia	10 (<1)	9 (2)	0	5 (1)	1 (<1)	25 (1)	7 (2)
Increased triglyceride level	11 (<1)	1 (<1)	0	11 (3)	2 (2)	25 (1)	5 (2)
Diarrhoea	6 (<1)	9 (2)	1 (<1)	8 (2)	1 (<1)	25 (1)	4 (1)
Pyrexia	9 (<1)	5 (1)	0	5 (1)	0	19 (<1)	0
Increased CPK level	17 (1)	0	0	0	0	17 (<1)	6 (2)
Headache	9 (<1)	1 (<1)	0	5 (1)	2 (2)	17 (<1)	4 (1)
Increased amylase	11 (<1)	0	0	3 (<1)	2 (2)	16 (<1)	2 (<1)
Pneumonia	8 (<1)	3 (<1)	0	5 (1)	0	16 (<1)	2 (<1)
Nausea	7 (<1)	3 (<1)	0	3 (<1)	1 (<1)	14 (<1)	7 (2)
Fatigue	4 (<1)	3 (<1)	1(<1)	4 (<1)	2 (2)	14 (<1)	3 (<1)
Abdominal pain	7 (<1)	4 (<1)	0	1 (<1)	1 (<1)	13 (<1)	0
Increased lipase level	1 (<1)	4 (<1)	2 (1)	5 (1)	1 (<1)	13 (<1)	0
Rash	9 (<1)	0	1 (<1)	2 (<1)	0	12 (<1)	2 (<1)
Vomiting	4 (<1)	3 (<1)	1 (<1)	4 (<1)	0	12 (<1)	2 (<1)
Upper abdominal pain	4 (<1)	0	1 (<1)	5 (1)	0	10 (<1)	1 (<1)
Dizziness	5 (<1)	0	0	1 (<1)	0	6 (<1)	6 (2)

a 3TC/ZDV/EFV.

APV = amprenavir; **CPK** = creatine phosphokinase; **d4T** = stavudine; **EFV** = efavirenz; **FPV** = fosamprenavir; **NFV** = nelfinavir; **RTV** = ritonavir; **ZDV** = zidovudine.

AEs Leading to Permanent Treatment Discontinuation

The AEs leading to permanent study drug discontinuation during the conduct of study are summarised in table IX. The incidence of AEs leading to premature discontinuation reported in each treatment group was distinct and ranged from 13 to 24% of patients in the various treatment groups. There was only a single AE that occurred in >1% of the total lamivudine/abacavir treatment group and led to treatment discontinuation, which was drug hypersensitivity. In comparison, it must be noted that reported AEs with >1% discontinuation rates in the lamivudine/zidovudine/efavirenz group were drug hypersensitivity, nausea, rash, vomiting, headache, malaise and anaemia. Overall, there were no significant trends across the studies other than discontinuation due to drug hypersensitivity, which has been well documented in prior clinical studies.

AEs of Special Interest

The most clinically significant AE associated with all abacavir-containing products is the drug-related abacavir hypersensitivity reaction that occurs in ≈5–8% of patients receiving abacavir.[29,30] Several manuscripts have detailed the abacavir hypersensitivity reaction and the overall incidence of this event in this analysis is consistent with previous reports.[38-41] Suspected abacavir hypersensitivity reactions reported by study investigators during the CNA30021trial[17] (abacavir once daily group 9%; abacavir twice daily group 7%) were similar in

terms of both incidence and clinical presentation compared with a historical cohort of 206 cases from nine clinical trials.[38] No unexpected abacavir hypersensitivity reaction safety concerns were reported with once daily or twice daily administration of abacavir by any patients within any of the clinical studies examined in this analysis.

Discussion

This analysis of safety-population data from five clinical studies demonstrates that multiple drug regimens using lamivudine/abacavir were generally well tolerated and that safety profiles were comparable over the duration of treatment exposure (≥48 weeks). Suspected abacavir hypersensitivity reactions reported by study investigators were similar in terms of both incidence and clinical presentation compared with historical data, regardless of the use of abacavir once daily or twice daily.[38-41] As previously described, reports of abacavir hypersensitivity reactions after week 48 were uncommon. There were no patient fatalities attributed by investigators to either study regimen during the conduct of these studies, nor any evidence indicating that lamivudine/abacavir contributed to any new unexpected adverse clinical manifestation.

In this analysis the distribution of patients who discontinued therapy during the minimum of 48 weeks of follow-up varied among treatment arms; the total lamivudine/abacavir group had a lower percentage of discontinuations due to AEs or lost to follow-up than the lamivudine/zidovudine/efavirenz group; however, these differences were not statistically different. Of note, the incidence of discontinuation due to insufficient viral load response was 3-fold higher in the total lamivudine/abacavir group (9%) than the lamivudine/zidovudine/efavirenz group (3%). This difference in discontinuation rates

Table VII. Number (percentage) of most common serious adverse events (SAEs) with lamivudine/abacavir (3TC/ABC)

SAEs	+ EFV n = 1191	+ NFV n = 409	+ FPV n = 166	+ RTV and FPV or APV n = 412	+ d4T n = 101	Total 3TC/ABC n = 2279	Control[a] n = 325
Patients with any SAE	209 (18)	83 (20)	29 (17)	79 (19)	16 (16)	416 (18)	46 (14)
Drug hypersensitivity	83 (7)	30 (7)	17 (10)	33 (8)	7 (7)	170 (7)	10 (3)
Pneumonia	12 (1)	4 (<1)	0	5 (1)	0	21 (<1)	2 (<1)
Hypersensitivity	16 (1)	1 (<1)	0	0	0	17 (<1)	2 (<1)[b]
Pyrexia	6 (<1)	3 (<1)	0	4 (<1)	0	13 (<1)	2 (<1)
Depression	5 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	9 (<1)	0
Diarrhoea	4 (<1)	1 (<1)	0	4 (<1)	0	9 (<1)	0
Vomiting	2 (<1)	2 (<1)	0	4 (<1)	0	8 (<1)	3 (<1)
Abdominal Pain	3 (<1)	2 (<1)	0	2 (<1)	0	7 (<1)	0
Dehydration	4 (<1)	2 (<1)	0	0	1 (<1)	7 (<1)	0
Suicidal ideation	6 (<1)	0	0	1 (<1)	0	7 (<1)	0
Suicide attempt	4 (<1)	1 (<1)	1 (<1)	0	0	6 (<1)	1 (<1)
Cellulitis	2 (<1)	0	0	4 (<1)	0	6 (<1)	1 (<1)
Appendicitis	4 (<1)	1 (<1)	0	0	0	5 (<1)	1 (<1)
Asthma	1 (<1)	0	1 (<1)	3 (<1)		5 (<1)	1 (<1)
Anaemia	0	2 (<1)	0	0	0	2 (<1)	4 (1)
Headache	0	0	0	2 (<1)	0	2 (<1)	4 (1)

a 3TC/ZDV/EFV.

b Ten patients initially reported having an ABC hypersensitivity reaction. However after investigators unblinded patients' treatment assignment, they determined that patients had not been exposed to ABC. After determination of treatment assignment investigators either deleted or recategorised initial ABC hypersensitivity reaction diagnosis to drug hypersensitivity: not ABC-related [3 (<1%)].

APV = amprenavir; **d4T** = stavudine; **EFV** = efavirenz; **FPV** = fosamprenavir; **NFV** = nelfinavir; **RTV** = ritonavir; **ZDV** = zidovudine.

Table VIII. Number (percentage) of fatal adverse events (all reported events) with lamivudine/abacavir (3TC/ABC)

Fatal adverse event	+ EFV n = 1191	+ NFV n = 409	+ RTV and FPV or APV n = 412	Control[a] n = 325
Patients with any event	10 (<1)	4 (<1)	6 (1)	3 (<1)
Sepsis	1 (<1)	1 (<1)	2 (<1)	0
Histoplasmosis	0	1 (<1)	0	0
Bacterial meningitis	0	0	0	1 (<1)
Pneumonia	0	1 (<1)	1 (<1)	0
Septic shock	0	1 (<1)	0	0
Lymphoma	2 (<1)	0	0	1 (<1)
Non-Hodgkin's lymphoma	1 (<1)	1 (<1)	0	0
Diffuse B-cell lymphoma	0	0	1 (<1)	0
Kaposi's sarcoma	0	0	1 (<1)	0
Cardiac arrest	2 (<1)	0	0	0
Acute myocardial infarction	1 (<1)	0	0	0
Cardiac failure	0	0	1 (<1)	0
Coronary artery atherosclerosis	1 (<1)	0	0	0
Death	1 (<1)	0	0	0
Oedema	1 (<1)	0	1 (<1)	0
Azotemia	1 (<1)	0	0	0
Renal failure	0	0	0	1 (<1)
Acute renal failure	1 (<1)	0	0	0
Status asthmaticus	0	0	1 (<1)	0
Hepatic failure	0	0	0	1 (<1)
Sudden infant death syndrome[b]	1 (<1)	0	0	0
Stillbirth	0	0	0	1 (<1)
Drug abuse	1 (<1)	0	0	0

a 3TC/ZDV/EFV.

b The single case of sudden infant death syndrome was attributed to the child born to the partner of a patient who was enrolled in the trial.

was primarily driven by the higher rates of insufficient viral load response in the lamivudine/abacavir/PI groups, where the study populations appeared to be of a more advanced disease state. This difference in response was not observed in any of the groups that contained a NRTI backbone plus efavirenz. Apparently, the more advanced disease state of patients in the PI-containing arms may have been because the fosamprenavir clinical studies had no CD4+ cell count entry criteria, which resulted in a lower median CD4+ cell count and a higher percentage of subjects with CDC Class C disease classification. The other studies had minimum CD4+ cell count requirements of at least 50–100 cells/mm^3 as part of the study entry criteria, which curtailed the number of patients with highly advanced HIV. Overall, however, all study populations were similar and reflective of treatment-naive study populations in other recent clinical programmes.[23]

The use of lamivudine/abacavir as an NRTI backbone as part of HAART in treatment-naive HIV-1-infected adults was tolerated and reflective of the current professional labelling.[29-31] The overall rates of AEs were similar among the various treatment arms. The distribution of AEs across each of the individual treatment groups was consistent with the known safety profiles of the third agents in each of the treatment groups.[32-35] Higher rates of nausea were associated with the PI usage, especially nelfinavir, and higher rates of dizziness, insomnia

and abnormal dreams were associated with efavirenz usage.

The total lamivudine/abacavir group had lower incidences of drug-related AEs when compared with the lamivudine/zidovudine/efavirenz group (p = 0.012 Fisher's exact test); this difference was driven mainly by nausea, vomiting, headache and fatigue, which have been reported with zidovudine treatment.[16,17] Nausea was the most common drug-related AE reported in 18% of patients receiving lamivudine/abacavir compared with 31% of patients in the control arm. When comparing the reported AEs between the lamivudine/abacavir/efavirenz group and the lamivudine/zidovudine/efavirenz group, the former group faired as good as or better than the latter in reports of low overall incidences of AEs. When considering drug-related adverse events, this difference was statistically significant (p = 0.02).

The most common drug-related AE specifically attributed to the lamivudine/abacavir combination was drug hypersensitivity that was reported in 7.7% (175 of 2279) of all patients. It must be noted that the five studies included in this analysis used an extensive data collection form for identification of detailed events and timings, regardless of number or severity of clinical symptoms. However, the limitation of this reporting method was observed in the clinical trial, CNA30024,[16] which compared the combination of lamivudine, abacavir and efavirenz

Table IX. Number (percentage) of adverse events (AEs) leading to permanent treatment discontinuation with lamivudine/abacavir (3TC/ABC)

AE leading to study drug discontinuation	+ EFV n = 1191	+ NFV n = 409	+ FPV n = 166	+ RTV and FPV or APV n = 412	+ d4T n = 101	Total 3TC/ABC n = 2279	Control[a] n = 325
Patients with any AE leading to study drug discontinuation	180 (15)	55 (13)	23 (14)	72 (17)	24 (24)	354 (16)	58 (18)
Drug hypersensitivity	82 (7)	30 (7)	16 (10)	33 (8)	7 (7)	168 (7)	10 (3)
Nausea	11 (<1)	4 (<1)	1 (<1)	6 (1)	4 (4)	26 (1)	11 (3)
Rash	15 (1)	1 (<1)	1 (<1)	5 (1)	0	22 (1)	10 (3)
Diarrhoea	7 (<1)	4 (<1)	0	7 (2)	1 (<1)	19 (<1)	0
Hypersensitivity	17 (1)	1 (<1)	0	0	0	18 (<1)	0
Vomiting	5 (<1)	3 (<1)	1 (<1)	4 (<1)	2 (2)	15 (<1)	8 (2)
Pyrexia	6 (<1)	3 (<1)	0	2 (<1)	1 (<1)	12 (<1)	0
Increased AST level	2 (<1)	3 (<1)	1 (<1)	4 (<1)	2 (2)	12 (<1)	1 (<1)
Dizziness	9 (<1)	1 (<1)	0	1 (<1)	0	11 (<1)	0
Fatigue	4 (<1)	2 (<1)	0	2 (<1)	3 (3)	11 (<1)	0
Increased ALT level	0	2 (<1)	1 (<1)	5 (1)	2 (2)	10 (<1)	1 (<1)
Abdominal Pain	4 (<1)	0	2 (1)	1 (<1)	1 (<1)	8 (<1)	3 (<1)
Headache	4 (<1)	0	0	2 (<1)	0	6 (<1)	7 (2)
Abnormal dreams	6 (<1)	0	0	0	0	6 (<1)	1 (<1)
Malaise	4 (<1)	0	0	0	1 (<1)	5 (<1)	7 (2)
Insomnia	5 (<1)	0	0	0	0	5 (<1)	3 (<1)
Anaemia	0	0	0	0	0	0	11 (3)

a 3TC/ZDV/EFV.

ALT = alanine aminotransferase; **APV** = amprenavir; **AST** = aspartate aminotransferase; **d4T** = stavudine; **EFV** = efavirenz; **FPV** = fosamprenavir; **NFV** = nelfinavir; **RTV** = ritonavir; **ZDV** = zidovudine.

with lamivudine, zidovudine and efavirenz, when, ten (10/325; 3%) cases of suspected abacavir hypersensitivity reaction were reported in the lamivudine/zidovudine/efavirenz treatment arm.[29] However, the guidance for the administration of abacavir within a blinded clinical trial, and the diagnosis and management of abacavir hypersensitivity reaction, are designed to be conservative and all-inclusive in determining observed incidences of abacavir hypersensitivity reaction. So, in using this approach the result is more likely to produce an abacavir hypersensitivity reaction rate that is greater than the true rate due to the inclusion of false-positives. There were no cases of hypotension reported as drug-related AEs in any of the treatment groups.

A broad understanding of abacavir hypersensitivity reaction has been acquired from multiple clinical trials, postmarketing experience, and non-clinical research activities. Approximately 500 000 patient-years of postmarketing experience have been generated during the past 5 years, as illustrated by the changes to the product labelling over time, where medical guidance to healthcare practitioners has progressed from a close surveillance of rash and fever to entail a more complete physical assessment of the syndrome through multiorgan system involvement.

Recently, reports have cited a strong association between presumed abacavir hypersensitivity reaction and *HLA-B**5701 allele carriage, reported mainly in Caucasian patients, by several groups.[42-45] As retrospective ascertainment of abacavir hypersensitivity reaction may be difficult, the clinical utility of *HLA-B**5701 screening in reducing abacavir hypersensitivity reaction is being investigated in a prospective, double-blind, multicentre clinical study that compares the abacavir hypersensitivity reaction rate between a current standard-of-care abacavir treatment group and a prospective pharmacogenetic screening group excluding subjects who carry the *HLA-B**5701 allele. Because the rate of abacavir hypersensitivity reaction and the allele frequency of *HLA-B**5701 differ among racial groups, alternative study designs may be needed to investigate the utility of *HLA-B**5701 screening for abacavir hypersensitivity reaction in non-Caucasian populations.[39-41]

In all, abacavir hypersensitivity reaction risk-management programmes strive to minimise risk, which includes communication of the benefit-risk profile in professional product labelling, educational opportunities and materials for healthcare professionals and for patients, a pharmacogenetics/genomic initiative and epidemiology programmes. In addition, many institutions have also adopted risk-management algorithms for the management of this AE.

The use of the combination of lamivudine/abacavir has been shown to have little or no effect on serum lipid levels in antiretroviral-naïve patients.[46] However, the use of NRTI combinations has been implicated in the development of the lipoatrophy component of the HIV lipodystrophy syndrome.[47-50] Lipoatrophy has been associated with cumulative duration of NRTI exposure and the current use of NRTIs with a greater propensity to inhibit mitochondrial DNA polymerase γ.[51-56] Prior study results suggest that initiation of an abacavir-based ART in the appropriate patients requiring NNRTI- or PI-based HAART maybe a useful strategy to decrease the likelihood of long-term metabolic complications associated with ART including hyperlipidaemia and lipoatrophy.[57] In other studies investigating lipid changes, clinical outcomes appear influenced to some degree by HIV-disease status, race and other patient baseline characteristics. In antiretroviral-naive patients, lamivudine/abacavir/zidovudine treatment has been shown to have little or no effect on serum lipids.[58-61]

Conclusion

The incidence of AEs, drug-related AEs, severe AEs or SAEs were often quite similar and rarely significantly different across the various lamivudine/abacavir treatment groups. When differences were noted, they were expected and consistent with known safety profiles of lamivudine/abacavir or the third agent used in the treatment regimen, with most AEs being mild to moderate in severity and self-limiting. Reported SAEs were typically low (<1%) with only abacavir hypersensitivity reaction occurring at >1%. The AEs and SAEs reported by patients from these clinical studies[15-19] were consistent with those reported in previous clinical trials.[29-35] No new safety issues have emerged with this combination that would distinguish it as significantly different to the most highly utilised nucleoside backbone combination of lamivudine/zidovudine/efavirenz.

Overall, the optimal long-term management of HIV-1 infection currently necessitates the long-term use of HAART that is highly effective, tolerated and that can preserve future treatment options.[9,10] This analysis indicates that the combination of lamivudine/abacavir is generally safe for the majority of patients when used as part of combination therapy.

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