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Review article

Triple-Nucleoside Analog Antiretroviral Therapy: Is There Still a Role in Clinical Practice? A Review

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Abstract

The development and widespread clinical use of coformulated abacavir/lamivudine/zidovudine (ABC/3TC/ZDV) as *Trizivir* represented an important advance in the management of HIV-infected patients, especially those with adherence challenges. With a low pill burden, no food restrictions, limited drug-drug interactions, and a favorable resistance profile, ABC/3TC/ZDV remains an alternative option in the US Department of Health and Human Services Consensus Panel Guidelines as initial treatment in antiretroviral-naive patients. Recent data have shown ABC/3TC/ZDV to be less efficacious in suppressing and/or maintaining suppression of virologic replication compared with efavirenz-containing antiretroviral therapy. Although triple-nucleoside/nucleotide reverse transcriptase inhibitor (t-NRTI) combinations that do not contain a thymidine analog (ZDV or stavudine) have recently shown high virologic failure rates in clinical trials and clinical practice, t-NRTI regimens containing a thymidine analog have consistently been shown to be efficacious.

Introduction

The development and widespread clinical use of coformulated abacavir/lamivudine/zidovudine (ABC/3TC/ZDV) as *Trizivir* represented an important advance in the management of HIV-infected patients, especially those with adherence challenges. With a low pill burden, no food restrictions, limited drug-drug interactions, and a favorable resistance profile, ABC/3TC/ZDV remains an alternative option in the US Department of Health and Human Services (DHHS) Consensus Panel Guidelines as initial treatment in antiretroviral-naive patients.[1] Recent data from the AIDS Clinical Trials Group (ACTG) 5095 study, however, have shown ABC/3TC/ZDV to be less efficacious in suppressing and/or maintaining suppression of virologic replication compared with efavirenz (EFV)-containing antiretroviral therapy (ART).[2] Recent data from clinical trials and clinical practice showing high virologic failure rates from a number of other triple-nucleoside/nucleotide reverse transcriptase inhibitor (t-NRTI) combinations[3-8] have led some clinicians to conclude that t-NRTI-based ART has a limited role, if any, in clinical practice. However, t-NRTI regimens containing a thymidine analog (ZDV or stavudine [d4T]) have consistently been shown to be efficacious.

This article will review the literature and examine the clinical role of t-NRTI-based ART as initial therapy, as switch therapy, and as part of induction-maintenance strategies.

Triple-Nucleoside Analogs Alone as Initial ART

The concept of using single-class ART as initial treatment of HIV is based on the potential to preserve future treatment options and to limit long-term side effects of other antiretroviral classes. In addition, the development of fixed-dose coformulation products such as *Trizivir* and 3TC/ZDV (*Combivir*) helped lower total daily pill burdens and potentially improve patient adherence. However, many clinicians are apprehensive about therapies that do

not target multiple sites of viral replication, especially for a virus such as HIV, with extremely high error-prone replication. This apprehension, coupled with high virologic response rates from combination ART regimens containing an NRTI backbone with either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) (single or boosted with ritonavir), has caused many clinicians to be cautious, and often confused, about using t-NRTI in current practice.

Recently, t-NRTI combinations that contain tenofovir (TDF) have been investigated in prospective and observational clinical trials and used in clinical practice. A number of these t-NRTI-based regimens have resulted in high virologic failure rates; of particular concern has been the frequent development of the K65R and/or M184V nucleoside mutations in viral isolates from patients treated with these regimens. It is, however, important to note that not all t-NRTI regimens are created equal; whereas certain t-NRTI regimens have shown high failure rates, others have not. The data for these various regimens will be reviewed separately to clarify differences between viable and nonviable t-NRTI combinations.

ABC/3TC/ZDV and ABC + 3TC + d4T

The most clinical experience with t-NRTI-based ART for initial treatment of HIV is with ABC/3TC/ZDV. Data from 2 large, randomized prospective clinical trials, CNA 3005 and CNA 3014, resulted in approval by the US Food and Drug Administration of ABC/3TC/ZDV for treatment of HIV.[9,10] These trials showed that the t-NRTI regimen is not as potent as PI-containing regimens, but that it provides a significant adherence benefit that compensates for potency in patients with baseline viral load < 100,000 copies/mL. In those with higher baseline viral loads, the t-NRTI regimen may not be as effective as PI-containing regimens. A third study comparing ABC/3TC/ZDV with EFV-containing 3- or 4-drug combinations in a blinded fashion found the EFV-based regimens to be more effective at suppressing viral replication and maintaining that suppression, regardless of baseline viral load, although the blinded comparison did not allow for real-world dosing of the t-NRTI regimen.

CNA 3005 was a prospective, multicenter, double-blind, placebo-controlled trial that randomized 562 treatment-naive HIV-infected patients with CD4+ cell counts > 100 cells/mcL and plasma HIV RNA > 10,000 copies/mL to receive ABC (300 mg twice daily) plus 3TC/ZDV (1 tablet twice daily) or 3TC/ZDV (1 tablet twice daily) plus indinavir (IDV; 4 capsules every 8 hours).[9] The blinded nature of the trial required a total of 16 pills to be taken daily. Groups were well matched, with the median CD4+ cell count and viral load at baseline approximately 360 cells/mcL and 70,000 copies/mL, respectively. At 48 weeks, median changes in baseline CD4+ cell counts were similar between groups, and an intention-to-treat (ITT) analysis found that equal proportions of patients had viral load measurements < 400 copies/mL (51% ABC + 3TC/ZDV vs 51% 3TC/ZDV + IDV). The as-treated analysis showed suppression to < 400 copies/mL in 86% and 94% of those in the ABC and IDV arms, respectively, 95% confidence interval (CI, -14, 0). Among patients with baseline viral loads > 100,000 copies/mL, 45/100 (45%) and 30/96 (31%) reached < 50 copies/mL (ITT) in the IDV and ABC arms, respectively, 95% CI (-27, 0). The difference in response to the ABC arm vs the IDV arm among patients with high baseline viral loads created interest in conducting a similar comparison in an open-label fashion, which would allow real-world dosing. Study CNA 3014 was designed to evaluate whether a potential adherence benefit with the triple-nucleoside regimen would compensate for concerns about potency with this combination.

CNA 3014 was a prospective, open-label, multicenter, equivalence (noninferiority) clinical trial that randomized 342 ART-naive HIV-infected patients with CD4+ cell counts > 100 cells/mcL and HIV RNA > 5000 copies/mL to receive 3TC/ZDV twice daily + ABC twice daily or 3TC/ZDV twice daily + IDV 800 mg 3 times daily.[10] CNA 3014 differed from CNA 3005 in that it was not blinded, resulting in a more "real-world" pill burden; patients receiving 3TC/ZDV + ABC took 4 tablets per day whereas those in the 3TC/ZDV + IDV arm took 8 tablets/capsules per day with food and fluid restrictions. Groups were well matched at baseline: median CD4+ cell counts were 331 cells/mcL for the 3TC/ZDV + ABC group (n = 169) and 299 cells/mcL for the 3TC/ZDV + IDV group (n = 173); the median plasma HIV RNA was 4.78 and 4.82 copies/mL for ABC- and IDV-treated patients, respectively. Equivalence of 3TC/ZDV + ABC and 3TC/ZDV + IDV was defined as a lower limit of the 95% CI > -15% for the difference between arms in suppression < 400 copies/mL at week 48. At 48 weeks, 3TC/ZDV + ABC met the criterion of equivalence: 66% of patients treated with 3TC/ZDV + ABC and 50% of those treated with 3TC/ZDV + IDV had HIV RNA < 400 copies/mL via ITT analysis; 95% CI (6.0, 27.2; P = .002) The ABC arm showed noninferiority in suppressing to < 400 copies/mL and < 50 copies/mL at all viral load strata, via ITT analyses. However, 67% of patients with baseline HIV RNA < 100,000 copies/mL and 48% of patients with baseline HIV RNA > 100,000 copies/mL who received 3TC/ZDV + ABC achieved viral load measurements < 50 copies/mL (ITT). In an as-treated, subgroup analysis that stratified patients by baseline viral loads, 73% and 59% of those with baseline viral loads > 100,000 copies/mL reached < 50 copies/mL in the IDV and ABC arms, respectively, 95% CI (-34.1, 5.2); among those with baseline viral loads between 5000 and 100,000 copies/mL, 90% and 87% in the ABC and IDV arms,

respectively, reached < 50 copies/mL, 95% CI (-7.5, 14.2). Changes in the mean absolute CD4+ cell count from baseline were similar between treatment groups (3TC/ZDV + ABC group: 148 cells/mcL vs 3TC/ZDV + IDV: 152 cells/mcL). The differences observed in this trial are believed to be a result of the pill burden/adherence benefit offered by the t-NRTI regimen, which may compensate for potency concerns in patients with baseline viral loads < 100,000 copies/mL, as evidenced by patient self-reported adherence (72% of 3TC/ZDV + ABC patients vs 45% of 3TC/ZDV + IDV patients reported missing more than 1 dose over the previous 4 weeks; $P < .001$).

A third trial, CNAF3007, compared coformulated 3TC/ZDV + ABC with 3TC/ZDV + nelfinavir (NFV) 3 times daily in an open-label, multicenter, randomized study of 195 treatment-naive HIV-infected patients.[11] At 48 weeks, similar proportions of ABC- and NFV-treated patients had HIV RNA < 50 copies/mL (55% for both treatment groups by ITT analysis). Although greater mean increases in CD4+ cell counts were observed among 3TC/ZDV + ABC-treated patients (137 cells/mcL) than among 3TC/ZDV + NFV-treated patients (88 cells/mcL), this was countered by the higher mean baseline CD4+ cell counts of patients receiving NFV compared with those who received ABC (471 vs 390 cells/mcL, respectively). As expected, there was a higher incidence of diarrhea (47% vs 7%) and a lower incidence of potential hypersensitivity reactions (0% vs 4%) among NFV-treated patients.

The studies described above compared ABC/3TC/ZDV with unboosted, high-pill-burden, frequent daily administration PI-based ART. Although beneficial, these regimens have been shown to be inferior to current nonnucleoside or pharmacokinetically enhanced boosted PI-containing ART. In Gilead's 903 trial, which compared d4T with TDF, both used in combination with 3TC and EFV, the overall proportion of patients with HIV RNA < 50 copies/mL was 74% and 78% for d4T- and TDF-treated patients, respectively.[12] In combination with d4T + 3TC, therapy with ritonavir-boosted lopinavir (LPV/r) produced viral response rates of 74% and 63% for HIV RNA < 400 and < 50 copies/mL, respectively.[13] One key trial, however, compared ABC/3TC/ZDV with EFV-containing ART. ACTG 5095 was a double-blind, placebo-controlled, multicenter trial that randomized, 1147 HIV-infected, antiretroviral-naive patients 1:1:1 to receive ABC/3TC/ZDV, 3TC/ZDV + EFV, or ABC/3TC/ZDV + EFV.[2] Groups were well matched, with a mean CD4+ cell count of 238 cells/mcL and HIV RNA of 4.85 $\log_{10}$ copies/mL (42% of patients had viral load measurements > 100,000 copies/mL). At the first interim analysis, the Data Safety Management Board halted the study because the t-NRTI underperformed when compared with the pooled EFV-containing arms, regardless of viral load strata. Of the 33% of patients who completed 48 weeks of treatment, 74% of ABC/3TC/ZDV-treated patients and 89% of EFV-treated patients had HIV RNA < 200 copies/mL; 61% and 74% had viral load measurements < 50 copies/mL, respectively. Among patients who achieved HIV RNA < 200 copies/mL at least once, the time to virologic failure was shorter in the t-NRTI arm than in the EFV arm ($P < .001$). In an analysis of the 780 patients with at least one HIV-1 RNA value < 50 copies/mL, a similar difference was suggested, but it was not statistically significant ($P = .08$).

The CLASS study evaluated the first-line regimens of ABC + 3TC + d4T, ABC + 3TC + EFV, and ABC + 3TC + amprenavir/ritonavir (APV/r) among 291 antiretroviral-naive patients.[14] The median baseline HIV RNA and CD4+ cell count were 4.9 $\log_{10}$ copies/mL (42% with viral load measurements > 100,000 copies/mL) and 299 cells/mcL, respectively. At 48 weeks, the EFV treatment arm demonstrated significant increases in the proportion of patients with HIV RNA < 50 copies/mL vs the other 2 treatment groups (76% for EFV, 59% for APV/r, and 62% for d4T; $P = .047$ by ITT analysis). These data again show that a t-NRTI regimen that contains a thymidine analog with 3TC and ABC has virologic efficacy comparable to that of a PI-based regimen, but inferior to that of an EFV-based regimen.

ZDV or d4T + ABC and 3TC as Initial ART: Discussion

Although data show that ABC may be equivalent to NFV and APV/r, and potentially superior to IDV, when combined with d4T or ZDV + 3TC, the overall response rates are lower than those seen in clinical trials comparing these t-NRTI regimens with EFV-containing ART, which is recommended as a preferred initial option in combination with 2 NRTIs by the DHHS guidelines.[1] The coformulation of the boosted PI, LPV/r, combined with 2 NRTIs, is the other regimen recommended by the DHHS guidelines as a preferred initial therapy.[1] In ACTG 5095, the overall rate of virologic success in the ABC/3TC/ZDV treatment arm (74% < 200 copies/mL) was considerable, albeit inferior to the pooled EFV arms. In 3 other large randomized, controlled clinical trials mentioned above, ABC + 3TC + ZDV consistently showed similar efficacy results.[9-11]

Although virologic suppression and durability of response are priorities of initial therapy, consideration must also be given to future treatment options if virologic failure occurs. The use of d4T or ZDV in combination with ABC and 3TC preserves classes, whereas EFV-based regimens often compromise future activity of at least 1 antiretroviral class. Among the 43 patients who experienced virologic breakthrough or were never fully virologically suppressed in CNA 3005, the development of any mutation other than M184V was infrequent.[15] Upon initial

virologic breakthrough, 84% of patients had an M184V or wild-type viral isolate on genotypic testing. Of the 28 patients who continued ABC + 3TC/ZDV despite having continued viral replication, the development of thymidine analog mutations (TAMs) was slow, with only 25% of isolates showing TAMs at 6 months. Similar results were seen among isolates evaluated from patients experiencing virologic failure on ABC/3TC/ZDV in ACTG 5095.[2] Of the 82 patients experiencing virologic failure on ABC/3TC/ZDV, 57% had M184V alone or wild-type virus, 11% had M184V plus an NRTI mutation, and 2% had NRTI mutations alone (27% had HIV RNA < 500 copies/mL and 4% could not be sequenced). In contrast, virologic failure with an EFV-based regimen has been shown to produce a high rate of NNRTI mutations that confer cross-resistance to the other agents in this class.

Consequently, initial therapy with ABC/3TC/ZDV or d4T + 3TC + ABC remains a viable option among patients unwilling to take EFV- or LPV/r-based ART. Among patients with baseline viral load measurements > 100,000 copies/mL, the benefits and convenience of ABC/3TC/ZDV must be weighed against its lower potency compared with those of NNRTI- or PI-based regimens. As suggested by the results of CNA 3014, the fixed-dose formulation of ABC/3TC/ZDV, with its lower pill burden, represents a potentially beneficial treatment option for patients with adherence-related issues. In contrast to NNRTI-containing ART, early treatment failure with ABC/3TC/ZDV or d4T + 3TC + ABC, which usually results from the development of the M184V mutation, creates little cross-resistance to other NRTIs.

Nonthymidine-Containing ("TAM-Sparing") t-NRTI Regimens as Initial ART

Clinical trials that have investigated the use of TDF as part of the NRTI backbone of an ART regimen among treatment-naive patients have shown this agent to be highly potent and well tolerated, with resultant durable treatment responses. Because TDF has potency against HIV when administered once daily with or without food, as well as a resistance profile different from that of ZDV and d4T, 2 TDF-containing once-daily t-NRTI regimens have been evaluated as initial ART.[3,6,8,16] Although these regimens have contained 3 nucleoside analogs highly potent against HIV, a number of prospective and observational trials have unfortunately shown high rates of treatment failure with viruses that contain the K65R and/or M184V mutation(s).

The largest prospective study to date has been GlaxoSmithKline's ESS30009 trial, which was a randomized, prospective, open-label, multicenter trial in antiretroviral-naive patients. The study evaluated the investigational fixed-dose formulation of ABC 600 mg plus 3TC 300 mg (ABC/3TC) given once daily in combination with either EFV 600 mg once daily or TDF 300 mg once daily.[6] A total of 194 patients were enrolled in the study when an interim analysis, conducted on patients who had received at least 8 weeks of therapy, demonstrated high rates of inadequate virologic suppression among patients receiving ABC/3TC + TDF. Of the 102 patients randomized to receive TDF, 50 (49%) failed to achieve either a 2-$\log_{10}$ copies/mL decrease from baseline or had a 1-$\log_{10}$ copies/mL or greater increase above the nadir viral load on any subsequent visit. In contrast, only 5 of 92 patients (5%) on ABC/3TC + EFV experienced inadequate virologic suppression. Among patients with defined virologic nonresponse to ABC/3TC + TDF who could be genotyped (n = 36), 23 (64%) had K65R plus M184V and 13 (36%) had M184V/I alone.

The TONUS trial studied the ABC + 3TC + TDF combination in 38 patients, with a median CD4+ cell count of 222 cells/mcL and a median viral load of 4.87 $\log_{10}$ copies/mL.[16] The study was stopped prematurely because of poor results: 12 (33%) of 36 enrolled patients experienced virologic failure by week 24. The response correlated with baseline viral load: Therapy failed in 64% of those with baseline viral loads > 5 $\log_{10}$ copies/mL, compared with 29% of those with viral loads between 4 and 5 $\log_{10}$ copies/mL, and none of the 8 patients with baseline viral loads < 4 $\log_{10}$ copies/mL. Among the 11 patients whose resistance data after virologic failure were available, 9 had both the M184V and K65R mutations and 2 had M184V alone. The investigators examined drug levels, because there has been speculation about whether drug interactions could explain the poor results seen with such regimens. The 4-week plasma C_{min} was adequate for all 3 drugs in 86% of patients, and there was no relationship between trough concentration and virologic response. Data on intracellular drug concentrations showed that the active triphosphate metabolites of at least one of the drugs were detected in all patients. These data suggest that the poor virologic outcome for this combination of drugs is not due to an adverse pharmacologic interaction.

Farthing and colleagues[3] presented data from a small prospective, observational, pilot study in which 19 antiretroviral-naive patients received once-daily ABC 600 mg, 3TC 300 mg, and TDF 300 mg. At week 8, 11 patients (58%) experienced treatment failure, defined as less than a 2-$\log_{10}$ decline from baseline in HIV RNA or viral rebound after initial suppression; only 5 patients were defined as treatment successes. Similar to the results of ESS30009, the majority of patients had M184V alone (n = 5) or M184V plus K65R (n = 4) on genotypic evaluation.

Recently, a small, prospective, open-label study of TDF + didanosine (ddI) + 3TC in 24 antiretroviral-naive patients

was terminated early because of high rates of virologic failure (91% of patients at 12 weeks); resistance testing of 21 patients revealed M184V/I in 20 patients, of whom 10 also had K65R.[8]

Several retrospective studies have evaluated the use of t-NRTI-based ART. Winston and colleagues[7] analyzed all genotypes within their clinic for K65R. K65R was associated with the antiretroviral combinations of ABC+ ddI + TDF or dual use of ddI + TDF-containing regimens. Of the 42 patients who received ABC + ddI + TDF and resistance testing (n = 22), 9 (41%) developed K65R. Patients who did not receive ABC + ddI + TDF or who concurrently received a thymidine analog were significantly less likely to develop K65R. Ruane and colleagues[4] identified 13 cases of K65R among 51 patients who received TDF-containing ART with expected or documented wild-type reverse transcriptase prior to initiation of TDF. The use of once-daily ABC + 3TC + TDF (n = 6) and ddI + 3TC + TDF (n = 3) accounted for most of the treatment failures. Genotypic testing demonstrated 10 patients with M184V plus K65R. MacArthur and colleagues[5] found that the combination of ddI + TDF (plus any other agent) was associated with an increased incidence of K65R compared with other combinations (12 of 182 patients; 6.6%).

Several potential explanations have been postulated as to why there have been such high failure rates among these nonthymidine analog t-NRTI-based regimens.[17] The most plausible explanation is the use of 3 NRTIs that both have low genetic barriers to selection of resistant viruses and select for the K65R and/or M184V mutations. In addition, as discussed above, the t-NRTI regimens are not as potent as NNRTI- or PI-based regimens, which may also contribute to the rapid selection of resistant virus with a subsequent high virologic failure rate. The most common regimens associated with high rates of early failure have included ABC + 3TC + TDF, ddI + 3TC + TDF, and ABC + ddI + TDF. All of these agents appear to have decreased activity against HIV with K65R in vitro. When any 2 of these NRTIs have been evaluated in combination regimens with either an NNRTI or a PI, these types of treatment failures have not been observed. This is likely due to the enhanced potency of these regimens and lowered selection pressure on the K65R and M184V mutant virus populations.

If t-NRTI is to be employed, these regimens should contain a thymidine analog, if possible. In vitro data suggest that K65R antagonizes primer unblocking, the main mechanism of resistance to thymidine analogs.[18] As a result, the thymidine analogs appear to be resensitized, and the use of thymidine analogs appears to decrease the likelihood of K65R development. If a thymidine analog cannot be used, an additional agent with activity against K65R should be employed (eg, an NNRTI or a boosted PI).

In conclusion, it cannot be overemphasized that clinicians should not use these inadequate t-NRTI regimens to treat HIV infection.

Triple Nucleosides Alone as Switch Therapy

In hopes of decreasing pill burdens, preserving future treatment options, and potentially lowering the risk of drug-induced adverse effects such as lipodystrophy and hyperlipidemia, many clinicians and investigators have switched patients from a fully suppressive NNRTI- or PI-containing regimen to a t-NRTI regimen. This strategy has only been proven effective in patients who had been virologically suppressed for an extended period at the time of the switch.[19-22] One of the most commonly investigated switch strategies has involved replacing a PI with ABC among patients receiving 2 other NRTIs, resulting in a triple-nucleoside regimen. Once again, however, clinicians should consider such a switch only if the t-NRTI regimen has been proven to be adequate.

CNA30017 was a randomized, multicenter, open-label study that enrolled 311 HIV-infected patients who were receiving 2 NRTIs plus a PI, had undetectable HIV RNA since starting ART, and were receiving current therapy for more than 6 months.[19] The enrolled patients either continued their current regimen (n = 103) or switched the PI to ABC (n = 104). Over time, a significantly greater number of continuation patients experienced treatment failure as opposed to those who switched to t-NRTI (n = 12, t-NRTI vs n = 24, continuation; $P = .03$). The main cause of treatment failure in the continuation arm was adverse drug events (n = 14); few patients in either arm experienced virologic failure (n = 4, t-NRTI vs n = 2, continuation).

TRIZAL was a randomized, prospective, open-label switch study that evaluated patients who were receiving any triple-ART regimen and had HIV RNA < 400 copies/mL for 6 or more months, had been on the same regimen for more than 6 months, and had HIV RNA < 50 copies/mL at screening.[20] Enrolled patients either continued their current therapy or the entire regimen was switched to ABC/3TC/ZDV; 103 continued their current regimens and 106 patients switched to ABC/3TC/ZDV. The groups were well matched at baseline; however, 15% of patients who switched to ABC/3TC/ZDV had received prior mono- or dual-NRTI therapy. At 48 weeks, 75% of ABC/3TC/ZDV-treated patients and 69% of continued therapy-treated patients had HIV RNA < 50 copies/mL via ITT analysis. Virologic rebound was infrequent; 5 ABC/3TC/ZDV-treated patients and 1 continued-therapy patient experienced HIV RNA > 400 copies/mL. Three of the 5 ABC/

3TC/ZDV-treated patients with virologic rebound had received prior mono- or dual-NRTI treatment.

Martinez and colleagues[22] randomized 460 patients who were receiving PI-containing triple-drug ART and had HIV RNA levels < 200 copies/mL for at least the previous 6 months to switch the PI to nevirapine (NVP, n = 155), EFV (n = 156), or ABC (n = 149). Groups were well matched at baseline with roughly one half of patients in each treatment arm having received mono- or dual-NRTI therapies prior to their PI-based ART. At 12 months, 10% of NVP-treated, 6% of EFV-treated, and 13% of ABC-treated patients reached a predefined endpoint of death, progression to AIDS, or HIV RNA > 200 copies/mL (P = .10). Fasting plasma triglyceride and cholesterol levels rose among all 3 treatment groups; however, ABC-treated patients had significantly lower increases compared with the NNRTI groups (P < .001). The rates of adverse drug events requiring study discontinuation were significantly higher among NNRTI-treated patients than among those who received ABC; however, no differences were observed between EFV and NVP. Among the 28 patients who received ABC and experienced virologic failure, 23 (82%) had received prior nonsuppressive ART with single or dual NRTIs alone. These data, as well as those from TRIZAL, show that if a patient is to be switched to t-NRTI, a thorough and detailed history of prior ART is necessary to prevent virologic breakthrough following the switch. It is also evident that a switch to ABC in patients who initiated HIV therapy with at least 3 drugs is a safe and effective strategy that is comparable to NNRTI-switch strategies.

The use of PI-sparing regimens has gained interest because many of the older PI-containing regimens often increase fasting cholesterol and triglyceride values and may cause lipoaccumulation disorders. The evaluation of switch therapy to t-NRTI has, therefore, been investigated among patients receiving PI-based ART who have hyperlipidemia. ESS40003 was an open-label pilot study that assessed antiretroviral efficacy and lipid changes among patients experiencing hyperlipidemia when switching from a PI to ABC.[23] Patients were included in the study if they had been on their current dual NRTI plus PI-based regimen for more than 3 months, had HIV RNA < 400 copies/mL on their last 2 consecutive clinic visits, had HIV RNA < 50 copies/mL and fasting total cholesterol > 200 mg/dL at screening, and were not currently receiving any cholesterol- or triglyceride-lowering medication. A total of 144 patients were randomized to either continue their current PI-based ART (n = 52) or switch their PI to ABC (n = 52). At 28 weeks, 62% of ABC-treated patients and 75% of continued PI-treated patients had HIV RNA < 50 copies/mL. There was no significant difference in time to treatment failure between the 2 arms (P = .397).[23] A careful evaluation of the causes of treatment failure showed that the majority of ABC failures occurred early following the switch and were a direct result of new or suspected adverse drug events; only 3 ABC-treated patients experienced virologic failure (defined as HIV RNA > 1000 copies/mL on 2 consecutive occasions). Compared with patients who continued PI therapy, patients switched to ABC experienced greater reductions from baseline in total cholesterol (-39 mg/dL vs -0.6 mg/dL; P < .001), low-density lipoprotein (LDL) cholesterol (-24 mg/dL vs -4 mg/dL; P = .016), and triglycerides (-109 mg/dL vs +47 mg/dL; P = .019).

The NEFA (nevirapine, efavirenz, abacavir) lipid substudy evaluated the fasting lipid profiles of 92 patients who were receiving stable PI-based ART (HIV RNA < 200 copies/mL for more than 6 months) and who were switched to NVP (n = 30), EFV (n = 33), or ABC (n = 29).[24] Data evaluating the effects of the switch on 69 patients following 24 months of treatment (n = 22 ABC, n = 21 EFV, n = 26 NVP) were recently presented. Patients who switched to either NVP or EFV had minimal changes in total cholesterol (NVP +2%; EFV, -6%), modest decreases in LDL cholesterol (NVP, -17%; EFV -10%), and significant increases in high-density lipoprotein (HDL) cholesterol (NVP, +50%; EFV, +12%). Patients who switched to ABC had significant decreases in total cholesterol (-13%) and LDL cholesterol levels (-15%). Triglyceride levels in all 3 groups remained relatively unchanged.

Because the efficacy of ABC/3TC/ZDV alone as initial therapy has been shown to be lower when the baseline HIV RNA is > 100,000 copies/mL, some clinicians are reluctant to switch patients on ART with nondetectable HIV RNA to ABC/3TC/ZDV if the baseline HIV RNA was > 100,000 copies/mL. Moyle and colleagues[21] retrospectively evaluated 32 patients who had received ART, achieved HIV RNA < 50 copies/mL, and were switched to ABC/3TC/ZDV despite baseline HIV RNA > 100,000 copies/mL prior to initiation of ART. The median pre-ART HIV RNA was 193,093 copies/mL with a median CD4+ cell count of 155 cells/mcL (12 of 32 [38%] had CD4+ cell counts < 100 cells/mcL). Patients had received initial ART for a median of 28 months prior to switch, with a median CD4+ cell count of 447 cells/mcL at the time of switch. After a median of 6.5 months from the time of switch to ABC/3TC/ZDV, no patient experienced virologic failure. Randomized, prospective clinical trials with long-term follow-up are needed to validate these encouraging findings.

A recent report evaluated the strategy of switching patients on stable ART to ABC + 3TC + TDF.[25] A retrospective evaluation of 8 patients without history of treatment failure on any prior antiretroviral regimen and on stable ART for a median of 14.2 months (range: 7.567.5 months) were switched to ABC + 3TC + TDF. Five of the 8 patients experienced virologic failure following the switch at a

median of 130 days; 4 of the 5 had the K65R mutation, the M184V/I mutation, or both. Consequently, the use of this regimen for simplification of therapy cannot be recommended.

Simplification With t-NRTI: Discussion

The use of t-NRTIs as switch therapy for patients receiving stable ART for simplification and/or improvement in lipid abnormalities has proven effective for patients who initiated a PI- or NNRTI-based regimen with at least 3 agents, regardless of baseline viral load. However, this strategy should be used in patients with little to no prior treatment with mono- or dual-NRTI therapies, as these patients are more likely to experience virologic breakthrough following the switch. In addition, the t-NRTI should be carefully selected. Most studies have a thymidine analog in combination with 3TC, with ABC substituted for a PI, with limited treatment failures. In contrast, switching to regimens with low genetic barriers (eg, ABC + 3TC + TDF) appears to confer a high risk for virologic breakthrough. Although ABC/3TC/ZDV has decreased activity when used as initial therapy in patients with baseline viral loads > 100,000 copies/mL, it appears that once the patient's virus is fully controlled (as evidenced by prolonged viral suppression), ABC/3TC/ZDV may provide durable treatment benefit in a simplification/switch strategy.

Triple Nucleosides Alone When Used for Maintenance Therapy

The concept of induction-maintenance has garnered interest from both clinicians and researchers. This strategy involves starting patients on potent ART and changing to a simpler, more convenient and potentially less toxic regimen once the viremia is controlled and the immune system reconstituted. In the past, these strategies have not produced good results, but this may have been because the maintenance regimens employed were not highly potent (eg, indinavir monotherapy, 3TC/ZDV alone). A number of prospective studies have shown benefit of quadruple-based ART (eg, ABC/3TC/ZDV + EFV) as initial therapy, especially among patients with high baseline viral load measurements. The concept of using ABC/3TC/ZDV as maintenance therapy following induction with quadruple-based ART has been investigated.

SUBURBS was a small open-label pilot study that evaluated the quadruple-based regimen of ABC/3TC/ZDV + EFV as initial ART for treatment-naive patients.[26] Following 48 weeks of treatment, patients with HIV RNA < 50 copies/mL and CD4+ cell counts > 100 cells/mcL (n = 20) were switched to ABC/3TC/ZDV alone. At 48 weeks following the switch, 85% of patients had maintained HIV RNA < 50 copies/mL with continued immunologic benefit, as evidenced by CD4+ cell count increases. In addition, significant declines in total cholesterol values were observed when EFV was discontinued (-29.1 mg/dL; P = .0002). Of the 3 patients who experienced treatment failure, only 1 had documented virologic failure that was not a result of poor adherence or an adverse drug event. A large, prospective, multicenter trial (ESS40013) is currently under way to evaluate induction with ABC/3TC/ZDV + EFV for 48 weeks followed by randomization to continued ABC/3TC/ZDV + EFV or a switch to ABC/3TC/ZDV alone.[27] To date, only data from the induction phase have been presented.

Although the concept of induction-maintenance with t-NRTI-based ART specifically ABC/3TC/ZDV alone appears promising, only limited data currently support its use. More information will be available in the near future when the maintenance phase of ESS40013 is completed and the data are reported.

Conclusion

Whereas recent data have cast doubt on the widespread use of t-NRTI-based ART in general, not all t-NRTI-based regimens are the same. Some regimens, such as ABC/3TC/ZDV and d4T + ABC + 3TC, have produced good results when used as initial therapy, for simplification, and potentially as a maintenance regimen in induction-maintenance strategies. When used as initial therapy, these regimens have been shown to be less potent than current NNRTI-based ART; however, when adherence is an issue, or when the patient is unwilling or unable to take NNRTIs, t-NRTI regimens remain viable options. When considering whether to use ABC/3TC/ZDV in patients with baseline HIV RNA > 100,000 copies/mL, clinicians should weigh the benefits of low pill burden and convenience vs decreased potency. Other t-NRTI regimens have produced high virologic failure rates when employed either as initial ART or as switch therapy. Regimens such as ABC + 3TC + TDF, ABC + ddI + TDF, and ddI + 3TC + TDF include agents that are highly potent against HIV but are limited by a low genetic barrier to resistance, especially to the cross-resistant K65R viral isolate. When t-NRTI regimens are desired, inclusion of a thymidine analog should be considered, because it appears that these agents decrease the risk of developing K65R.

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