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Regimen Simplification to Atazanavir-Ritonavir Alone as Maintenance Antiretroviral Therapy: Final 48-Week Clinical and Virologic Outcomes

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Abstract

Background—Simplified maintenance therapy with ritonavir-boosted atazanavir (ATV/RTV) alone is attractive because of nucleoside reverse-transcriptase inhibitor (NRTI)–sparing benefits, low pill burden, once-daily dosage, and safety.

Methods—Subjects with virologic suppression after ≥48 weeks of initial antiretroviral therapy with 2 NRTIs and a protease inhibitor (PI) were enrolled. Subjects switched to ATV/RTV at entry and discontinued NRTIs after 6 weeks. The primary end point was time to virologic failure (confirmed HIV-1 RNA level ≥200 copies/mL). Drug resistance at virologic failure was evaluated by standard genotyping and single-genome sequencing (SGS). Residual viremia (1.1– 49 copies/mL) was measured by single-copy assay.

Results—Thirty-four subjects simplified to ATV/RTV alone, of whom 30 (88%) did not experience virologic failure by 48 weeks after simplification. Residual viremia did not change significantly after

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NRTI discontinuation among those without virologic failure but did increase 4 –12 weeks before confirmed virologic failure. No major PI-resistance mutations were identified at virologic failure by standard genotyping or SGS.

Conclusions—In this pilot study, simplified maintenance therapy with ATV/RTV alone maintained viral suppression in most subjects through 48 weeks. PI resistance was not detected among subjects experiencing virologic failure. Larger, randomized trials are warranted to further define the efficacy and safety of this strategy.

Combination therapy with at least 3 antiretroviral agents is the current standard of care for HIV-1 infection [1]; such therapy is maintained indefinitely in the absence of compelling reasons for discontinuation. The long-term toxicities, cost, and difficulty of sustained adherence to combination therapy have prompted investigation of simplified maintenance regimens. A series of small pilot studies [2–4] and randomized clinical trials [5–7] suggest that ritonavir (RTV)– boosted protease inhibitors (PIs) alone without other antiretroviral medications hold promise for such a strategy. RTV-boosted atazanavir (ATV/RTV) is an attractive option given its once-daily dosage, tolerability, and less-disadvantageous effects on lipids [8,9].

AIDS Clinical Trials Group (ACTG) protocol 5201 was a prospective, open-label, single-arm pilot trial of simplified maintenance therapy with ATV/RTV alone after sustained virologic suppression. The primary analysis was published previously [10]: 31 (91%) of 34 subjects maintained virologic suppression through 24 weeks after simplification. The present article reports the final 48-week results for the trial and the results of more-sensitive assays for drug resistance and residual viremia (HIV-1 RNA level) <50 copies/mL.

METHODS

The general methods for this study have been reported in detail elsewhere [10] and are summarized here.

Trial design: open-label, prospective, single-arm pilot trial of regimen simplification to ATV/RTV alone after sustained virologic suppression

Institutional review board approval was obtained at each of the 12 participating clinical sites. All subjects provided written informed consent, and the human-experimentation guidelines of the US Department of Health and Human Services were followed in the conduct of this research. The primary objective was to evaluate the risk of virologic failure, defined as 2 consecutive HIV-1 RNA measurements ≥200 copies/mL after simplification to ATV/RTV alone. Secondary objectives included safety and tolerability, detection of PI resistance–associated mutations at virologic failure, changes in residual plasma HIV-1 RNA level, lipid levels and CD4 cell counts, the relationship between plasma ATV concentrations and self-reported adherence or virologic outcomes. This protocol was registered at ClinicalTrials.gov (NCT00084019).

Eligibility criteria

Eligible subjects were aged 18 years or older, were receiving their first antiretroviral therapy regimen (defined as at least 2 nucleoside reverse-transcriptase inhibitors [NRTIs] plus at least 1 PI for at least 48 weeks before entry), had a CD4 cell count >250 cells/μL, and had a plasma HIV-1 RNA level <50 copies/mL for at least 48 weeks before entry. Subjects were excluded if they had received nonnucleoside reverse-transcriptase inhibitors previously, had a history of documented PI resistance, or were positive for hepatitis B surface antigen (because NRTIs may have been needed for the treatment of hepatitis B).

Study treatment

At entry, subjects discontinued their current PI and began taking ATV (300 mg daily) with RTV (100 mg daily). Subjects who had treatment-limiting toxicities or a detectable plasma HIV-1 RNA level 3 weeks after entry were discontinued from the study. Otherwise, subjects discontinued their NRTIs 6 weeks after entry and simplified therapy to ATV/RTV alone. Subjects were followed up for 48 weeks after simplification.

Study follow-up

Subjects had monthly follow-up visits for clinical assessments and plasma HIV-1 RNA measurements. Plasma samples for ATV concentrations were collected 12–24 h after the last dose of ATV. ATV concentrations were measured using previously reported methods [10]. The lower limit of detection for the high-performance liquid chromatography method used to quantify ATV concentrations was 20 ng/mL. Adherence was also measured using the ACTG self-report questionnaire [11].

Virologic analyses

For resistance testing, plasma samples with an HIV-1 RNA level >500 copies/mL from subjects with protocol-defined virologic failure and from 1 subject with an HIV-1 RNA level >500 copies/mL at the final study visit were analyzed using both standard genotyping (ViroSeq; version 2.6; ABI) and single-genome sequencing (SGS). For SGS analyses, we sought to obtain 45 or more sequences per sample to have 90% power to detect a resistant variant comprising 5% of the viral population. SGS analyses were performed as described elsewhere [12]. All 297 nt of the protease gene were sequenced by the dideoxyterminator method (ABI). Sequences were analyzed for protease-resistance mutations by means of the Stanford Drug Resistance Database and the International AIDS Society–USA drug-resistance mutation list [13,14].

For residual viremia, plasma samples from 13 study subjects were analyzed using a single-copy assay (SCA) with a detection limit of 1.1 copies/mL, as reported elsewhere [15]. This included 8 subjects without virologic failure, 4 with virologic failure, and 1 with an HIV-1 RNA level >200 copies/mL at the last study visit. All were known to have HIV-1 RNA that could be amplified efficiently by SCA (10 from participation in another clinical trial with pretherapy [16] and 3 subjects with virologic rebound).

Statistical analyses

The primary end point was time to virologic failure, defined as 2 consecutive plasma HIV-1 RNA measurements ≥200 copies/mL. The study was designed with 85% power to detect a difference between week 24 success rates of 75% with ATV/RTV alone versus a nominal rate of 90%, assuming an 8% dropout rate. The Kaplan-Meier method was used to estimate the distribution of the time from simplification (i.e., discontinuation of NRTIs) to virologic failure. The censoring time was defined as the time from simplification to the last HIV-1 RNA measurement. Subjects who left the study before simplification were excluded from this analysis. Greenwood's variance was used to estimate the lower 90% 1-sided confidence interval (CI) limit for the probability of virologic success at 48 weeks after simplification. A relaxed type I error of 0.1 was chosen for the primary end point because this was a pilot study. All other CIs and *P* values were 2-sided.

HIV-1 RNA levels for subjects analyzed by SCA for residual viremia were compared by descriptive and nonparametric analyses. For independent groups, the Wilcoxon-Mann-Whitney *U* test (for continuous outcomes) and Fisher's exact test (for binary outcomes) were used; for comparing continuous outcomes between time points within subjects, the Wilcoxon signed-rank exact test was used.

RESULTS

Baseline characteristics and subject disposition

Thirty-six subjects were enrolled from September 2004 through April 2005. Baseline characteristics are shown in table 1. Two subjects discontinued the study before simplifying to ATV/RTV alone: one because of scleral icterus and the other because of a plasma HIV-1 RNA level of 50 copies/mL. Thirty-four subjects simplified therapy to ATV/RTV alone. Two of the 34 subjects discontinued the study follow-up before 48 weeks because of an inability to attend study visits: one was followed up for 8 weeks after simplification to ATV/RTV alone and the other for 36 weeks.

Primary end point

Four subjects had confirmed virologic failure while receiving ATV/RTV alone, at 12, 12, 20, and 28 study weeks after simplification. The Kaplan-Meier estimate of the probability of virologic success at week 48 was 0.88 (lower 90% 1-sided CI limit, 0.81). Plasma HIV-1 RNA levels at the time of virologic failure were 4730, 1285, 28,397, and 626 copies/mL, respectively. In one other subject, the plasma HIV-1 RNA level was 508 copies/mL at the final study visit. Because this value was not confirmed, criteria were not met for protocol-defined virologic failure. A sensitivity analysis including this subject decreased the probability of virologic success to 0.84 (lower 90% 1-sided CI limit, 0.76). When a confirmed HIV-1 RNA level ≥50 copies/mL was used as a more-stringent definition of virologic failure, the probability of virologic success was 0.82 (lower 90% 1-sided CI limit, 0.73).

One subject with virologic failure at week 12 continued to receive ATV/RTV alone. Two other subjects continued to receive ATV/RTV and restarted NRTIs (tenofovir/emtricitabine). One subject discontinued ATV/RTV and initiated lopinavir (LPV)/RTV with tenofovir/emtricitabine. All 4 subjects subsequently achieved a plasma HIV-1 RNA level <50 copies/mL, but 2 of the 4 subjects had an intermittently detectable plasma HIV-1 RNA level during follow-up.

For the 30 subjects without virologic failure, plasma HIV-1 RNA levels over the course of the study were below the limit of detection (<50 copies/mL) in 304 (95%) of 321 samples collected during receipt of ATV/RTV alone. The 17 samples with detectable HIV-1 RNA levels were distributed among 9 subjects: 12 samples had 50 –199 copies/mL, and 5 had unconfirmed measurements ≥200 copies/mL.

Drug-resistance analysis

No major PI-resistance mutations were detected by standard population genotyping analyses for the 4 subjects with confirmed virologic failure or for the subject with viremia >200 copies/mL at the last study visit. SGS analysis was performed on failure samples from all 5 of these subjects. An average of 47 (range, 43–53) genomes per sample was analyzed to determine the presence of polymorphisms and resistance mutations in protease. No major PI mutations were identified in any of the 236 single-genome sequences analyzed, but several minor PI mutations and polymorphisms were identified. For 2 subjects, I64V was detected in 2 of 100 sequences combined, and G73S was detected in 2 of 90 sequences from 2 other participants. None of the minor mutations or polymorphisms identified by SGS was predicted to alter susceptibility to ATV.

Residual viremia

Plasma samples from 13 subjects were tested by SCA to determine the effects of regimen simplification on residual viremia (table 2). The median level of residual viremia in subjects without virologic failure (n = 8) was <1.1 copies/mL (interquartile range, <1.1 to 2.4 copies/

mL). There was no statistically significant difference in median residual viremia between study entry and after 48 weeks among subjects without virologic failure ($P = .219$, Wilcoxon signed-rank exact test). By contrast, the level of residual viremia increased in all 5 subjects with virologic failure or rebound 4 –12 weeks before HIV-1 RNA was detectable (>50 copies/mL), as determined by standard assay (table 2).

Pharmacokinetic/adherence analysis

Thirty-one (91%) of 34 subjects had detectable ATV concentrations at every measurement while receiving ATV/RTV alone. Among the 3 subjects with at least 1 ATV concentration below the limit of detection, 2 (67%) developed virologic failure, whereas, among the 31 subjects with detectable ATV at every measurement, two (6%) developed virologic failure ($P = .03$, Fisher's exact test). The median ATV level among subjects with virologic failure was 380 ng/mL, compared with 660 ng/mL among those without virologic failure ($P = .18$, Wilcoxon rank-sum test). Changes in ATV concentrations did not correlate with changes in residual viremia among subjects with virologic failure (data not shown).

Adverse events

Seventeen of 34 subjects had grade 3 or 4 increases in total bilirubin level. One grade 3 elevation in lipase level and 1 grade 3 elevation in phosphorus level were observed. No AIDS-defining illnesses occurred. CD4 cell counts did not change appreciably during the course of the study. Overall, lipid levels did not change significantly from the time of initiating ATV/RTV plus 2 NRTIs to 48 weeks after discontinuing NRTIs.

DISCUSSION

The present pilot study suggests that simplified maintenance therapy with ATV/RTV alone can maintain virologic suppression in most patients with prior virologic suppression who were receiving a PI-based regimen with 2 NRTIs. Moreover, major PI-resistance mutations did not develop in the 4 subjects with virologic failure or in the 1 subject with an HIV-1 RNA level >200 copies/mL at the final study visit, as determined by either standard population genotyping or the more-sensitive method of SGS. Subjects with virologic failure were more likely to have study visits with undetectable ATV concentrations. This strongly suggests that suboptimal adherence was an important factor in the development of virologic failure.

Among subjects without virologic failure, 95% of plasma HIV-1 RNA measurements were <50 copies/mL. This is similar to what was observed in ACTG 5095, a recent large, double-blind, placebo-controlled trial of 3 different antiretroviral regimens for initial treatment of HIV-infected subjects [17,18]. Among subjects in ACTG 5095 without virologic failure (same definition as the present study), 93% of HIV-1 RNA measurements obtained during the second year of antiretroviral therapy were <50 copies/mL (H. Ribaudo, personal communication).

In the present study, we monitored residual viremia <50 copies/mL by SCA in longitudinal samples before and after simplification of therapy in a subset of study subjects with or without virologic failure. The median level of residual viremia did not increase significantly after simplification of therapy among subjects without virologic failure, whereas increases in residual viremia were detectable by SCA 4 –12 weeks before rebound was evident by a standard HIV-1 RNA assay. Although the number of observations is small, the findings are consistent with published data from a prior pilot study of maintenance therapy with LPV/RTV alone [19] and suggest that more-sensitive HIV-1 RNA assays can be used to identify impending virologic failure with sufficient lead time to allow therapeutic intervention (e.g., adherence counseling and reinitiation of NRTIs). As noted above, monitoring of drug levels may also identify those at risk for virologic failure.

The present study adds to a growing body of data that simplified maintenance therapy with a boosted PI alone is effective in maintaining virologic control after initial suppression with a 3-drug regimen. Other studies of simplification have evaluated maintenance regimens with ATV, indinavir, and LPV, each boosted with RTV [2–7,20]. In these studies, similar proportions of subjects maintained virologic suppression as that observed in the present study. It should be noted, however, that one study of ATV/RTV alone was stopped early because it reached predefined stopping rules for suboptimal efficacy (5 of 15 subjects with virologic failure, defined as confirmed plasma HIV-1 RNA level >20 copies/mL) [20]. However, that study differed from ours in that patients were allowed to continue medications with known adverse pharmacologic interactions with ATV and used an HIV-1 RNA level of >20 copies/mL to define virologic failure.

Concern exists about increased risk of virologic failure, possibly associated with the development of PI resistance, after simplification to ATV/RTV or another RTV-boosted PI alone. This has been an infrequent event, noted in <2% of subjects in trials of simplified maintenance therapy [2–7,20].

The present study has several limitations. It was a pilot study and did not have a randomized control group. The population was highly selected in that they had received antiretroviral therapy for a median of 6.8 years without a prior history of virologic failure. The follow-up performed in this study was more frequent than would be done in clinical practice. As a result, the time spent with ongoing viremia for subjects with virologic failure was minimized. Development of drug resistance may occur with longer periods of viremia. The residual viremia testing was performed on a nonrandom sample of subjects without virologic failure, which could have introduced bias. However, this selection of subjects with pretherapy samples available ensured that undetectable HIV-1 RNA by the SCA was due to viral suppression rather than inefficient polymerase chain reaction amplification.

Simplified maintenance therapy challenges the current paradigms for treatment of HIV-1 infection and should be evaluated carefully. The risk of viral rebound during receipt of ATV/RTV or other RTV-boosted PIs alone may be greater than that during continuation of a standard 3-drug regimen. This would have long-term adverse consequences only if PI resistance develops or if resuppression of viremia is not achieved after reinitiating NRTIs, which has been infrequent and was not observed in our study. A higher risk of viral rebound may be balanced by the possibility of durable simplified therapy and decreased exposure to other drug classes. Indeed, Schackman et al. [21] have modeled the long-term outcomes of ATV/RTV maintenance therapy, compared with those of a standard 3-drug regimen, and found that the simplified strategy provided cost and survival advantages if the frequency of PI resistance and cross-resistance was low. However, this strategy cannot be recommended for clinical practice until large, adequately powered randomized trials are performed.

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Table 1
Baseline subject characteristics.

Characteristic	Value
Sex	
Male	33 (92)
Female	3 (8)
Race/ethnicity	
White/non-Hispanic	22 (61)
Black/non-Hispanic	9 (25)
Hispanic	4 (11)
Asian/Pacific Islander	1 (3)
Age category	
20–29 years	2 (6)
30–39 years	16 (44)
40–49 years	13 (36)
50 years and above	5 (14)
Time receiving ART, median (IQR), years	6.8 (4.2–7.0)
CD4 cell count, median (IQR), cells/μL	616 (443–756)
Nadir CD4 cell count, median (IQR), cells/μL	253 (71–456)
Prior PI therapy	
Atazanavir	3
Indinavir-ritonavir	2
Lopinavir-ritonavir	20
Nelfinavir	10
Saquinavir	1

NOTE. Data are no. (%) of subjects, unless otherwise specified. ART, antiretroviral therapy; IQR, interquartile range; PI, protease inhibitor.

Table 2

Single-copy assay (SCA) and ultrasensitive assay results for plasma HIV-1 RNA level in a subset of subjects without virologic failure and in subjects with confirmed or unconfirmed virologic failure participating in AIDS Clinical Trials Group protocol 5201.

	Weeks receiving ATV/RTV alone										
Group, subject, assay	**−6[a]**	**0[b]**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**48**
Those without virologic failure											
1											
SCA	<1.1	<1.1	<1.1	<1.1	<1.1	…	…	1.2	…	…	33.0
Ultrasensitive	<50	<50	<50	<50	<50	…	…	<50	…	…	<50
2											
SCA	<1.1	<1.1	<1.1	<1.1	<1.1	…	…	<1.1	…	…	1.2
Ultrasensitive	<50	<50	<50	<50	<50	…	…	<50	…	…	<50
3											
SCA	<1.1	<1.1	<1.1	<1.1	<1.1	…	…	<1.1	…	…	<1.1
Ultrasensitive	<50	<50	<50	<50	<50	…	…	<50	…	…	<50
4											
SCA	2.4	<1.1	<1.1	4.9	3.7	…	…	<1.1	…	…	<1.1
Ultrasensitive	<50	<50	<50	<50	<50	…	…	<50	…	…	<50
5											
SCA	2.8	<1.1	<1.1	<1.1	<1.1	…	…	151.1	…	…	24.8
Ultrasensitive	<50	<50	<50	<50	<50	…	…	122	…	…	145
6											
SCA	7.3	9.5	<1.1	12.6	9.4	…	…	23.0	…	…	14.7
Ultrasensitive	<50	<50	<50	<50	<50	…	…	<50	…	…	<50
7											
SCA	<1.1	2.9	2.4	1.5	<1.1	…	…	<1.1	…	…	NA
Ultrasensitive	<50	<50	<50	<50	<50	…	…	<50	…	…	NA
8											
SCA	1.5	<1.1	NA	<1.1	<1.1	…	…	<1.1	…	…	NA
Ultrasensitive	<50	<50	<50	<50	<50	…	…	<50	…	…	51
Median HIV-1 RNA by SCA	<1.1	<1.1	<1.1	<1.1	<1.1	…	…	<1.1	…	…	7.95
Those with confirmed or unconfirmed virologic failure											

Group, subject, assay	Weeks receiving ATV/RTV alone										
	−6[a]	0[b]	4	8	12	16	20	24	28	32	48
1											
SCA	<1.1	<1.1	q<1.1	7.9	**1272.3**	**254.5**	…	…	…	…	…
Ultrasensitive	<50	<50	<50	<50	**1285**	**304**	…	…	…	…	…
2											
SCA	12.9	4.2	52.4	217.1	**8637.6**	NA	…	…	…	…	…
Ultrasensitive	<50	<50	<50	153	**4730**	**669**	…	…	…	…	…
3											
SCA	<1.1	<1.1	2.9	<1.1	<1.1	22	**631.9**	**3461.3**	…	…	…
Ultrasensitive	<50	<50	<50	<50	<50	<50	**28,397**	**21,652**	…	…	…
4											
SCA	<1.1	<1.1	<1.1	3.7	<1.1	…	…	…	…	…	…
Ultrasensitive	<50	<50	<50	<50	<50	<50	<50	62	**626**	**669**	…
5											
SCA	<1.1	<1.1	<1.1	<1.1	NA	5.5	NT	<1.1	NT	3.1	NA
Ultrasensitive	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	508
Median HIV-1 RNA by SCA	<1.1	<1.1	<1.1	3.70	636.5	18.9	*	45.5	*	*	*

NOTE. Data are HIV-1 RNA copies/mL. The subset of subjects without virologic failure had pretherapy plasma samples available for SCA. Boldface type indicates HIV-1 RNA values at confirmed virologic failure (defined as 2 consecutive HIV-1 RNA measurements ≥200 copies/mL), and asterisks indicate that <3 SCA values were available to calculate the median. ATV/RTV, RTV-boosted atazanavir; NA, sample not available; NT, sample not tested; NRTIs, nucleoside reverse-transcriptase inhibitors; RTV, ritonavir.

[a] Subjects were previously receiving an antiretroviral regimen (protease inhibitor with or without RTV and 2 NRTIs).

[b] All subjects were receiving ATV/RTV and 2 NRTIs just before discontinuing NRTIs.