ART De-intensification to ATVr Monotherapy in Adolescents Sustains CD4 and Activation Responses

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ABSTRACT

Background: Adolescents and young adults infected with HIV face a lifetime of antiretroviral therapy (ART). Toxicities to antiretroviral therapy persist, including negative effects on bone renal function, and lipids; thus, limiting ARV exposure may still be of benefit. Assessing the impact of such interventions requires an understanding of their influence on viral suppression and T cell reconstitution and immune activation.

Methodology: 75 subjects, ages 18-24, with CD4 T cells >350 were started on FTC/TDF/ATVr as part of a randomized, unblended trial of therapy de-intensification. Subjects who maintained an HIV viral load (VL) <100 copies from weeks 24 through 48 were de-intensified to ATVr monotherapy at week 52 and to week 152. Subjects failed de-intensification for a confirmed VL>400 copies or confirmed CD4 drop of >30% from the average of the two peak values. Markers of T lymphocyte differentiation/activation were analyzed by multi-parameter LSR II flow cytometry to define naïve, central memory (CM), and effect or memory (EM) CD45RA and CD45RO subpopulations. Slopes of changes in T cell subsets and T cell activation from weeks 48 to 152 were estimated by a mixed effects model using a t-test to test whether mean slopes equaled zero.

Results: 49 of 75 subjects met criteria at week 48 of ART for de-intensification. 25 of 49 (51%) remained suppressed on monotherapy to week 152. Total CD4 gains during ART persisted during de-intensification with ongoing significant increases in naïve and CM (p=0.0167 and 0.0186, respectively) and a decrease in EMRA (p=0.0007) subsets from weeks 48 to 152. No significant changes occurred during monotherapy in any CD8 subpopulations. The significant increases in CD28 expression and decreases in CD38 and HLADR expression on CD8 subpopulations during ART were maintained during monotherapy without any significant increases to from week 48 through week 152. In 19 subjects failing de-intensification due to rebound virus, none demonstrated ATV resistance. Adherence was similar in those failing monotherapy up to the point of failure compared to those maintaining suppression.

Conclusion: In subjects treated with ART with CD4> 350, de-intensification to monotherapy with 48 weeks of ART is effective in maintaining naïve and CM CATVr following D4 T cell reconstitution. No ATV resistance was noted in subjects with confirmed virologic failure. No increases in immune activation were found in those maintaining viral suppression. This strategy merits further investigation to determine its appropriateness in selected populations.

BACKGROUND

- Infection with HIV continues to significantly impact adolescents and young adults in the US
- Earlier initiation of antiretroviral therapy (ART) is now recommended for most HIV-infected individuals
- Behaviorally HIV-infected youth may have unique responses to ART compared to adults due to 1) functional thymus glands; 2) shorter duration of infection; 3) less underlying intrinsic inflammation
- Data are limited on treatment outcomes in this population with even less data on de-intensification strategies
- ATN 061 studied therapy de-intensification in subjects initiating ART with CD4+T cells>350 cells/mm^3 who achieved virologic suppression by week 24 and maintained suppression through week 48

METHODS

Study Design and Population

- Behaviorally infected youth, 18 to 24 years of age, with CD4+ T cells > 350 cells/mm3 were recruited to the study
- Subjects were randomized in a 3:1 manner to either initiate ART with atazanavir/ritonavir plus TDF/FTC or to begin a provider-selected standard regimen of ART according to DHHS guidelines in effect at the time of the study
- Subjects who achieved a VL below 100 copies/mL by week 24 and maintained it through week 48 were de-intensified to monotherapy with ATVr at week 52 and followed to week 152
- Subjects failing de-intensification for virologic failure were defined as a VL>400 copies/mL confirmed by a second one six weeks later and had genotypic testing performed for VL>1000 copies/mL
- Group A11: subjects who maintained viral control out to week 152 on de-intensification; Group A12: subjects who failed de-intensification for any reason
- Cell differentiation/activation was analyzed with a multi-parameter LSR ll flow cytometer
- T cell subsets were defined as follows
  - o T helper cells (CD4): CD3+CD4+
  - o Cytotoxic T cells (CD8): CD3+CD8+
  - o Naïve CD4+ and naïve CD8+: CCR7+ and CD45RA+.
  - o Central memory CD4+ and central memory CD8+ (CM): CCR7+ and CD45RA-
  - o CD4+ effector memory RA and CD8+ effector memory RA (EMRA): CD45RA+ and CCR7-
  - o CD4+ effector memory RO and CD8+ effector memory RO (EMRO): CD45RA- andCCR7-

Soluble factor analyses for sCD14, sCD163 and sCD27 were performed utilizing commercially available ELISA kits

Statistical analysis: Descriptive statistics were computed. Slopes for expression of immunological factors during the specified study periods were estimated using a mixed effect model and were subsequently tested for whether the slope equals zero. Differences in expression of immunological factors between study time points (baseline vs. week 48, baseline vs. week 152, and week 48 vs. 152) were calculated and paired t-tests were used to test whether the differences equal zero. Statistical significance was set as p-value<0.05. All p-values were two-sided. Data analyses were performed using SAS v9.3 (SAS Institute, Cary, NC).

OBJECTIVES

- To determine if CD4+ T cell subpopulation gains during ART are maintained during therapy de-intensification to Atazanavir/ritonavir (ATVr)
- To determine if improvements in immune activation during ART are maintained during therapy de-intensification to ATVr
- To determine the impact of therapy and de-intensification on sCD14, sCD27 and sCD163.

RESULTS

TABLE 1

Variable	Group A1			
	Overall A1	Group A11	Group A12	p-value (A11 vs. A12)
Age (years)				
18-20	21(42.86)	13(52.00)	8(33.33)	0.2516
21-24	28(57.14)	12(48.00)	16(66.67)	
Gender				
Male	43(87.76)	22(88.00)	21(87.50)	1.0000
Female	6(12.24)	3(12.00)	3(12.50)	
Race/ethnicity				
Non-Hispanic	34(69.39)	15(60.00)	19(79.17)	0.4260
Hispanic	12(24.49)	8(32.00)	4(16.67)	
Asian or Other	3(6.12)	2(8.00)	1(4.17)	
Route of HIV transmission				
Male-to-male sexual contact	40(81.63)	19(76.00)	21(87.50)	0.2599
High-risk heterosexual contact	8(16.33)	5(20.00)	3(12.50)	
Unknown or Other	1(2.04)	1(4.00)	0(0.00)	
Baseline CD4$^+$ T-cell count (cells/mm^3)				
350 – 500	21(42.86)	9(36.00)	12(50.00)	0.3931
> 500	28(57.14)	16(64.00)	12(50.00)	
Baseline viral load (copies/ml)				
N	49	25	24	
Mean	21331.1	22669.0	19937.4	0.6620
SD	21544.6	23103.6	20192.7	

Table 1

- Subjects were predominantly male (88%) with slightly higher numbers in the 21-24 compared to 18-20 age group
- Approximately half the population (57%) had - baseline CD4+T cells >500 cells/mm3
- Men who have sex with men was the most common mode of HIV transmission
- Of 75 subjects randomized to group A, 48 subjects met criteria for de-intensification
- 21 of 48 discontinued study intervention after week 48: viral load failure (5), CD4 + T cell decline (2), adherence issues (5), toxicity (1), acute hepatitis B infection (1), move out of area (2), lost to followup (1), sclera icterus (1), and disallowed medications (1)

FIGURE 1

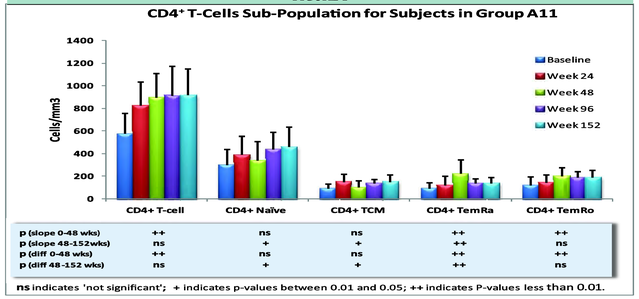


Figure 1

- Total CD4+ T cell gains achieved during 48 weeks of ART were maintained following de-intensification
- Significant expansion of CD4+ naïve and CM populations continued during de-intensification
- Significant contraction of CD4+ EMRA populations occurred during de-intensification with no significant changes in CD4+EMRO RO

FIGURE 2

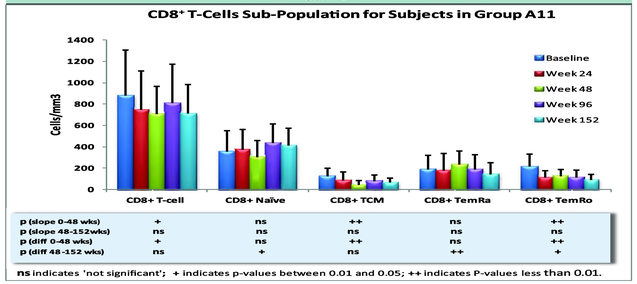
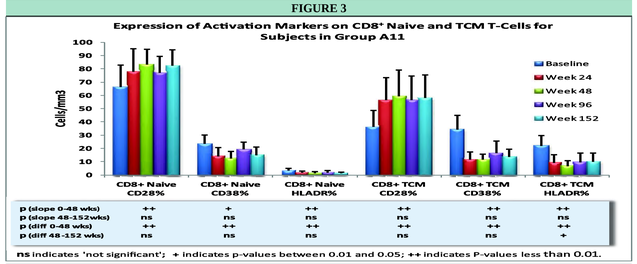


Figure 2

- Total CD8+ T cell decreases during ART were maintained during de-intensification
- Significant expansion of naïve CD8+ T cells during ART continued through de-intensification
- Decreases in CD8+ CM cells during ART were maintained during de-intensification
- No significant changes in CD8+ EM RA were noted but significant decreases during ART in EM RO were maintained during de-intensification

FIGURE 3



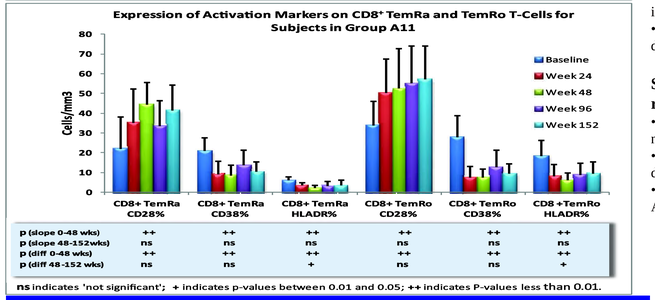


Figure 3

- CD28% expression increased during ART and was maintained during de-intensification for CD8+ naïve, EMRA, and EMRO while it continued to significantly increase in CM
- CD38% expression and HLA-DR% expression decreases on CD8+ naïve, CM, EMRA, and EMRO were maintained during de-intensification; however, when comparing mean percent expression at week 48 compared to 152, some significant increases were noted in HLA-DR% expression on CM, EMRA, and EMRO. Similar patterns were not seen for CD38% expression. were not seen for CD38% expression.

Soluble Factors:

- sCD14 and sCD27 levels were not impacted by ART or de-intensification in either A11 or A12 groups
- sCD163 decreased during ART with no significant changes during de-intensification in either A11 and A12 groups

Summary for subjects failing de-intensification for any reason:

- Of the five subjects with viral load failure, no ATV resistance was noted on genotypic analysis
- Significant improvements in CD4+ T cell subpopulations made during ART were maintained between weeks 48 and 152
- Decreases in immune activation markers on CD8+ T cells during ART were maintained from weeks 48 to 152

CONCLUSIONS

De-intensification in those who maintain viral control has no negative impact on CD4+ T cell reconstitution and improves naïve and central memory reconstitution

- De-intensification does not lead to any consistent increase in immune activation
- Increases in CD28 expression were maintained during de-intensification indicating sustained CD8+ T cell function
- In those failing de-intensification for viral load rebound, none demonstrated ATV resistance indicating failure due to adherence
- In those failing de-intensification for any reason, CD4+ T cell subset and immune activation were not negatively impacted
- ART was not associated with improvements in sCD14 or sCD27; however, sCD163 decreased significantly during ART with no changes during de-intensification

ACKNOWLEDGEMENTS

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