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Impact of RAL/MVC Intensification With or Without HIV-rAd5 Vaccination on HIV DNA: EraMune 02

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BACKGROUND: HIV eradication may require synergistic interventions that purge latent reservoirs and increase the HIV-specific cellular immune response. DNA prime followed by recombinant adenovirus 5 boost vaccination (HIV-rAd5) has been shown to induce strong CD8+ cytotoxic T lymphocyte responses in HIV-infected and uninfected individuals.

METHODOLOGY: Randomized, controlled, non-comparative clinical trial of ART intensification (raltegravir and maraviroc (RAL/MVC)) with or without HIV-rAd5. We included patients having: ≥3 years of HIV-1 RNA ≤500 copies/mL, HIV-1 RNA <40 copies/mL zone year, current CD4+ cell count ≥350/mm^3, HIV-1 DNA between 10 and 1,000 copies/10^6 PBMCs and serum Ad5 neutralizing antibody titer ≤ 250. After a lead-in of RAL/MVC intensification for 8 weeks, patients were randomized (1:1) to continue intensification with HIV-rAd5 vaccination [DNA prime at W8-W12-W16 and rAd5 boost at W32 (RAL/MVC/HIV-rAd5 arm)] or continue intensification alone (RAL/MVC arm) for 48 weeks. The primary end-point was >0.5 $\log_{10}$ decrease in HIV-1 DNA at 56 weeks. Secondary end-points included changes in rectal tissue HIV-1 DNA, immunologic changes in peripheral blood and rectal tissue, and safety.

RESULTS: We enrolled 28 patients (14 in each arm) on suppressive ART with the following median baseline characteristics: 636 CD4+ cells/mm^3, 672 CD8+ cells/mm^3, 170 HIV-1 DNA copies/10^6 PBMCs, 13 years on ART, and 2.6 years with HIV-1 RNA<40 copies/mL. At week 56, one patient in the RAL/MVC alone arm reached the primary endpoint with a 0.55 $\log_{10}$ decrease in HIV-1 DNA from 156 (W0) to 44 (W56) DNA copies/10^6 PBMCs. Mean PBMC and rectal tissue cell-associated HIV-1 DNA levels did not significantly change after RAL/MVC intensification with or without HIV-rAd5 injections (see table 3). Peripheral blood CD4+ and CD8+ cell counts did not significantly change from baseline to W56 in either arm (see table 4). RAL/MVC intensification and HIV-rAd5 vaccination were well tolerated and there were no serious SAEs related to study treatment.

CONCLUSIONS: RAL/MVC intensification with HIV-rAd5 vaccination did not reduce the total HIV DNA reservoir in either peripheral blood or rectal tissue. RAL/MVC intensification alone decreased the HIV-1 reservoir by over 0.5 log DNA copies/10^6 PBMCs in one patient.

Background

Eradication of HIV from an infected individual cannot be achieved by current potent antiretroviral therapy (ART). HIV eradication may require synergistic interventions that purge latent reservoirs and increase the HIV-specific immune response. DNA prime followed by recombinant adenovirus 5 boost vaccination (HIV-rAd5) has been shown to induce strong CD8+ cytotoxic T lymphocyte responses in HIV-infected and uninfected individuals. Our hypothesis was that viral eradication in selected HIV-infected patients is possible with intensification of ART plus immunomodulation with DNA prime/HIV-rAd5 boost vaccine.

Methods

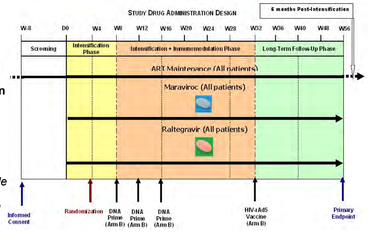
The EraMune 02 trial was a multicenter, randomized, non-comparative controlled study of ART intensification plus DNA prime/HIV-rAd5 boost vaccine in HIV-1 infected patients with long-term viral suppression.

❑ Study design

After a lead-in of raltegravir/maraviroc (RAL/MVC) intensification for 8 weeks, subjects were randomized (1:1):

ARM A (RAL/MVC): Continue intensification alone for 48 weeks

ARM B (RAL/MVC + DNA prime/HIV-rAd5 boost): Continue intensification for 48 weeks + DNA prime/HIV-rAd5 boost vaccination *[3 injections of HIV DNA prime coding for clade B Gag, Pol, and Nef and clade A, B, and C Env, followed by a replication-deficient adenovirus type 5 boost encoding all DNA vaccine antigens except Nef]*



❑ Eligibility Criteria

- Adults (≥18 and <70 years) with HIV-1 infection
- ≥3 years of HIV RNA ≤500 copies/mL and HIV-1 RNA <40 copies/mL ≥ one year
- 10 ≤ Proviral DNA ≤ 1000 copies/10^6 PBMCs within 75 days of entry
- CD4+ count ≥ 350 cells/mm^3 within 60 days of entry
- Adenovirus neutralizing antibody titer ≤ 250
- Not previously exposed to immunologic therapeutic intervention and no active hepatitis B or C

❑ Methods

- As in phase II cancer trials, with 14 evaluable patients in the intervention arms, if no patient succeeds, it means that the success rate is lower than 20% and the strategy is not worth pursuing. If there is at least one response, then additional studies are needed
- Success was defined as a decrease from baseline in HIV proviral DNA at week 56 of at least 0.5 log copies/10^6 PBMCs
- Cell HIV-DNA was quantified by ultrasensitive real-time polymerase chain reaction (PCR) (Generic HIV DNA Cell, Biocentric®Kit)
- T-cell responses to vaccine antigens were determined using a validated ELISpot assay
- Patients were monitored every 4 weeks for 56 weeks
- One additional visit follow-up was performed at week 80 (off all interventions)
- Wilcoxon paired test was used to compare the change in continuous variables between baseline, week 56, and week 80 in each arm

Results

Figure 1: Patient Flowchart

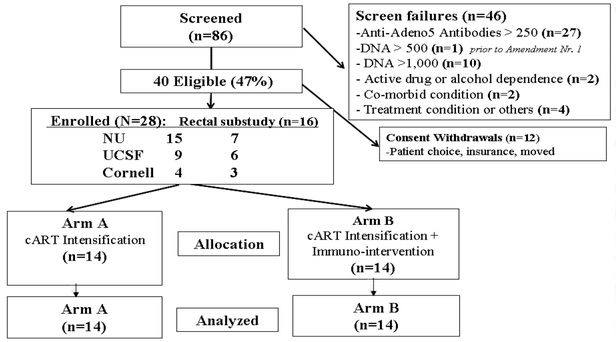


Figure 2: Change in HIV DNA ($\log_{10}$ copies/10^6 PBMCs)

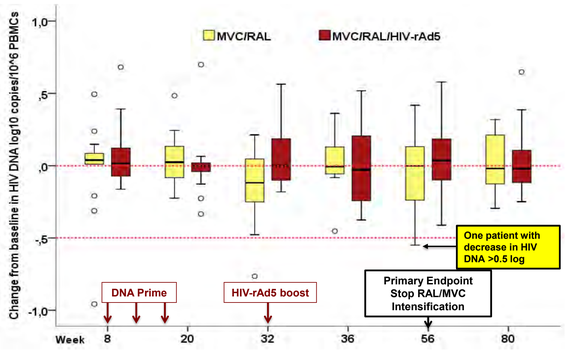


Figure 3: Change in CD4 count (cells/mm^3)

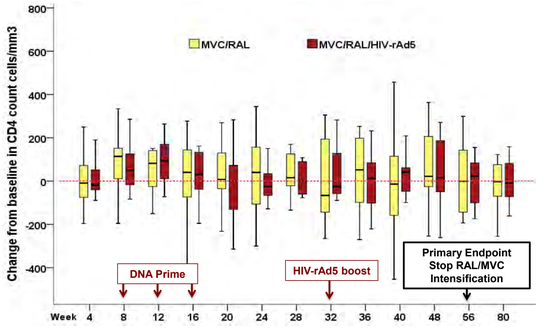


Figure 4: HIV specific T-cell responses

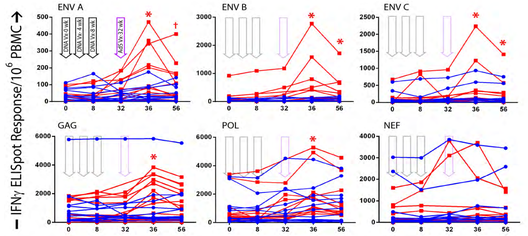


Table 1: Baseline Characteristics

Median (IQR)	RAL/MVC (n = 14)	RAL/MVC+ HIV-rAd5 (n = 14)	Total (n = 28)
Age, years	49 (46-55)	50 (46 – 55)	50 (46 – 55)
Sex, % Male	100%	100%	100%
Race , % White	79%	64%	71%
Time on cART, years	13 (8 – 19)	13 (6 – 19)	13 (8 – 19)
Prior AIDS events, n (%)	3 (21 %)	3 (21 %)	6 (21 %)
CD4 nadir (cells/mm^3)	220 (146 - 419)	179 (50 - 219)	202 (88 - 280)
CD4 count (cells/mm^3)	686 (501 - 880)	563 (468 – 718)	636 (485 – 791)
CD8 count (cells/mm^3)	625 (475 – 925)	719 (535 – 796)	672 (516 – 817)
Adeno-5 antibody titer	18 (12-68)	12 (12-38)	12 (12-41)
VL<50 cp/mL, %	100%	100%	100%
Duration of VL < 50 cp/mL (years)	2.4 (2.3 – 3.1)	2.7 (2.1 – 3.0)	2.6 (2.2 – 3.0)
HIV DNA copies/10^6 PBMCs	97(47 – 352)	228 (98 – 383)	170 (60 – 361)
ART regimen, n (%) -2 NRTIs + PI/r -2 NRTIs + NNRTI -NRTI+NNRTI+PI/r -NNRTI + PI	4 (39 %) 10 (71 %)	7 (50 %) 5 (36 %) 1 (7 %) 1 (7 %)	11 (39 %) 15 (54 %) 1 (4 %) 1 (4 %)

Table 2: Safety -- Serious Adverse Events

Study Treatment	Serious Adverse Event	Related to Study Treatment	Outcome
RAL/MVC	Creatinine Kinase (Gr. 4)	Possible (RAL)	Resolved without sequel
RAL/MVC + HIV-rAd5	Acute coronary syndrome	No (Hx of CAD)	Stents placed
RAL/MVC + HIV-rAd5	Renal Failure	Unlikely (only temporal association with HIV-rAd5 boost)	Hemodialysis
RAL/MVC + HIV-rAd5	Deep Vein Thrombosis	No	Resolved without sequel

- *No severe, moderate or systemic post-vaccine reactions to either DNA prime or HIV-rAd5 boost*
- *Patients reported mild post-vaccine reactions including tenderness, redness, and swelling at injection site*

Table 3: Median (IQR) Change in HIV DNA (Baseline to Week 56) in Blood Compartments and Rectal Tissue

		W0	W56	Δ W56-W0	p-value (W0 vs W56)
HIV DNA $\log_{10}$ copies per million PBMCs	RAL/MVC (n= 14)	2.32 (2.11-2.51)	2.33 (1.98-2.60)	0.00 (-0.29-0.16)	0.730
	RAL/MVC+ HIV-rAD5 (n=14)	2.46 (2.17-2.94)	2.58 (2.09-2.97)	0.04 (-0.11-0.10)	0.463
HIV DNA $\log_{10}$ copies per million CD4 cells	RAL/MVC (n= 12)	2.62 (2.43-2.87)	2.63 (2.39-3.04)	-0.02 (-0.24-0.20)	0.754
	RAL/MVC+ HIV-rAD5 (n=12)	2.84 (2.44-3.21)	2.87 (2.23-3.31)	-0.02 (-0.17-0.18)	0.937
HIV DNA $\log_{10}$ copies/mL Whole blood	RAL/MVC (n= 12)	2.68 (2.50-3.01)	2.72 (2.52-3.04)	-0.06 (-0.25-0.28)	1.000
	RAL/MVC+ HIV-rAD5 (n=12)	2.78 (2.40-3.16)	2.86 (2.14-3.24)	0.07 (-0.23-0.16)	1.000
HIV DNA $\log_{10}$ copies/mL (mean (SD) change) Rectal tissue	RAL/MVC (n= 7)	2.12 (0.42)	2.26 (0.39)	0.14 (0.27)	0.176
	RAL/MVC+ HIV-rAD5 (n=6)	2.38 (0.58)	2.44 (0.29)	0.06 (0.37)	0.917

Table 4: Mean (SD) Changes in CD4/CD8 Count (Baseline to Week 56)

Cell count/mm^3		W0	W56	Δ W56-W0	p-value (W0 vs W56)
Total CD4	RAL/MVC (n= 14)	749 (221)	799 (315)	50 (248)	0.889
	RAL/MVC+ HIV-rAD5 (n=14)	578 (148)	583 (151)	5 (112)	0.972
Total CD8	RAL/MVC (n= 12)	821 (407)	856 (363)	35 (248)	0.889
	RAL/MVC+ HIV-rAD5 (n=12)	750 (334)	717 (308)	-33 (150)	0.600
CD4/CD8 Ratio	RAL/MVC (n= 12)	1.24 (0.99)	1.15 (0.78)	-0.09 (0.31)	0.972
	RAL/MVC+ HIV-rAD5 (n=12)	0.93 (0.47)	0.92 (0.39)	-0.01 (0.14)	0.753

Conclusions

- RAL/MVC intensification with or without HIV-rAd5 vaccination **did not significantly reduce the total HIV DNA reservoir in either peripheral blood or rectal tissue**
  - RAL/MVC intensification alone decreased the HIV-1 reservoir by over 0.5 log DNA copies/10^6 PBMCs in only one patient
- There was **no significant effect** of RAL/MVC intensification with or without HIV-rAd5 vaccination **on CD4 or CD8 cell counts**
- DNA prime with HIV-rAd5 boost vaccination **was safe and induced significant T-cell responses against Gag, Pol, and Env** in HIV-infected patients on long-term suppressive ART
  - This vaccine should be studied further in combination with HIV latency reversal interventions as a novel eradication strategy

The EraMune 02 Study Group

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