Immune recovery following the addition of fostemsavir in virally suppressed immunologic non-responders living with HIV-final 48-week results from the RECOVER study

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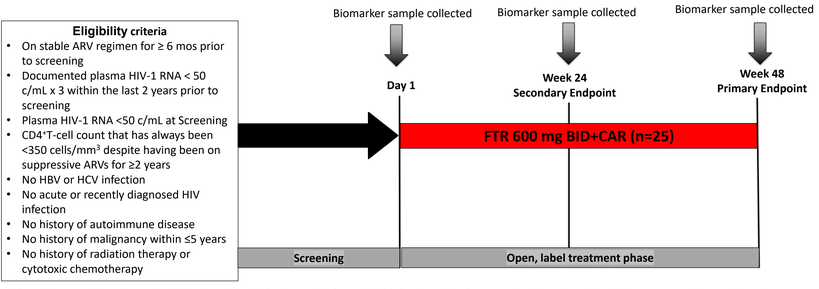
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BACKGROUND:

- Immunologic non-responders (INRs) are defined as people living with HIV (PLWH) with a persistent CD4⁺ T-cell count<350 cells/mm³ despite achieving sustained viral suppression for at least two years. INRs are at an increased risk of progression to AIDS, experience a higher burden of non-AIDS events and have higher mortality than PLWH who have achieved adequate immune reconstitution [1]
- Incomplete immune reconstitution has been linked to persistent and exacerbated immune activation which leads to reduced CD4⁺ T-cell production, increased CD4⁺ T-cell destruction, and increased T-cell exhaustion and senescence[2]
- In vitro data suggests that temsavir may inhibit innate immune activation incited by gp120 and protect uninfected CD4⁺T-cells from bystander killing[3]
- Interim analyses of the RECOVER study demonstrated significant increases in CD4⁺ T-cell count after the addition of fostemsavir (FTR) to baseline regimens among virally suppressed immune INRs through Week 48. Here, we present results from the full analysis set which included 25 enrolled participants.

METHODS:

RECOVER (NCT05220358) was a prospective open-label clinical trial of virologically suppressed adult INRs



Abbreviations. ARV, antiretroviral HBV, hepatitis B infection; HCV, hepatitis C infection; FTR, fostemsavir; BID, twice daily; CAR, current antiretroviral regimen

- Study utilized commercial insurance to pay for FTR and labs and visit schedule is designed to mimic routine clinical care (q3 month assessments)
- Co-primary endpoints are mean and median change in CD4⁺ T-cell count at Week 48 using pre-FTR mean and median CD4⁺ T-cell counts 96 weeks prior to study entry as controls. Mean and median CD4+ T-cell parameter changes were compared using the Student's t-test and Wilcoxon signed-rank test respectively
- Secondary endpoints include mean and median change in CD4⁺ percentage after addition of FTR at Week 48 using pre-FTR mean and median CD4+ percentage values 96 weeks prior to study entry as controls, mean change in CD4/CD8 ratio from baseline at Week 48 and proportion with CD4⁺ T-cell count greater than 200 and 350 cells/mm³ at Week 48
- Clinical safety including adverse events (AEs) and drug-relatedness were also evaluated

RESULTS:

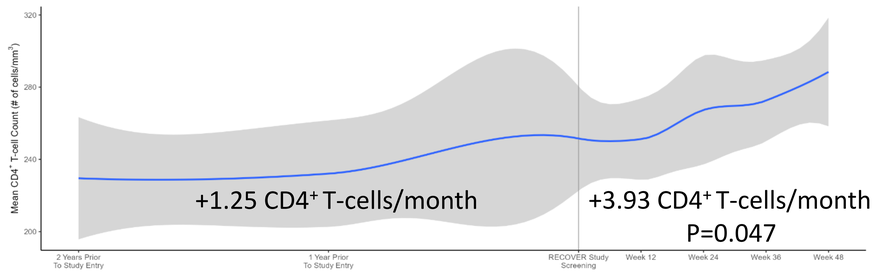
Table 1. Baseline demographic and clinical characteristics

Characteristic	FTR+CAR N=25
Median Age (range)	56 (38-64)
Sex	
Male, n (%)	20 (80)
Female, n (%)	5 (20)
Race	
Caucasian, n (%)	18 (72)
Black, n (%)	7 (28)
Ethnicity	
Hispanic/Latino, n (%)	9 (36)
Not Hispanic/Latino, n (%)	16 (64)
CD4⁺ T-cell count, mean/median (range), cells/mm³	248/252 (140-348)
Baseline CD4+ T-cell count	
<200 cells/mm³	8 (32)
201-349 cells/mm³	17 (68)
Duration of HIV infection, mean (range), years	23.8 (6-40)
Duration of ARV therapy, mean (range), years	23.6 (6-40)
Duration of viral suppression, mean (range), years	17.7 (3-38)
Baseline Anchor ARV class	
NNRTI	2 (8)
PI	3 (12)
INSTI	18 (72)
Multi-class regimen	2 (8)

Abbreviations. FTR, fostemsavir; CAR, current antiretroviral regimen; ARV, antiretroviral; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor

RESULTS cont'd:

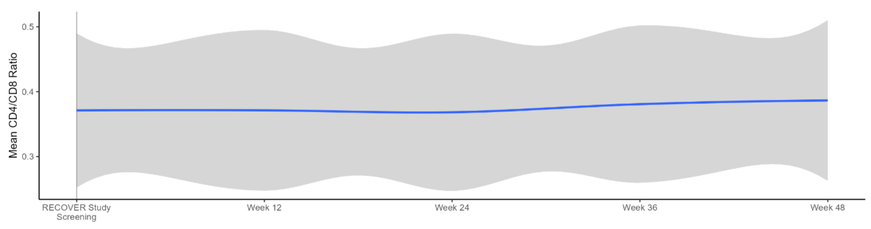
Figure 1. Mean CD4⁺ T-cell count 2 years prior to study entry through 48 weeks in the RECOVER study



*Shaded gray area denotes 95% confidence interval

At Week 48, mean and median CD4⁺ T-cell count significantly increased by 38 cells/mm³ and 28.7 cells/mm³ compared to pre-FTR controls (p=0.015 for mean and 0.016 for median). Increases in mean and median CD4⁺ percentage of 0.4% and 0.9% compared to pre-FTR controls (p=0.428 for mean and 0.228 for median) were also observed. At Week 48, the addition of FTR was associated with a gain of +3.93 CD4⁺ T-cells/month compared to a gain of +1.25 CD4⁺ T-cells/month pre-FTR (difference +2.68 CD4⁺ T-cells/month, p=0.047)

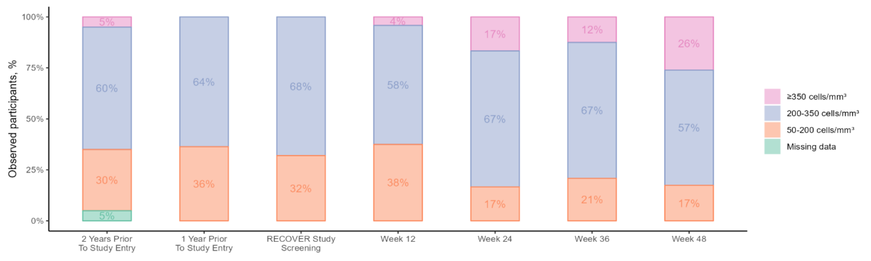
Figure 2. Mean change from baseline in CD4/CD8 ratio at Week 48



*Shaded gray area denotes 95% confidence interval

At Week 48, mean change from baseline in CD4/CD8 ratio was +0.012 (p=0.495))

Figure 3. CD4+ T-cell count change by category through 48 weeks in the RECOVER study



*5% of participants had a single CD4⁺ T-cell count value≥350 cells/mm³ 2 years prior to study entry that was considered to be a spurious outlier value

At Week 48, the proportion with CD4⁺ T-cell count ≥200 and ≥350 cells/mm³ was 83% and 26% respectively

Virologic Outcomes
Through Week 48, 3 participants had confirmed HIV-1 RNA between 50 and 200 copies/mL and 1 had confirmed HIV-1 RNA>200 copies/mL (suspected nonadherence) however, all resuppressed on FTR plus the baseline ARV regimen

Table 2. Adverse Events through Week 48

AEs, n (%)	FTR+CAR N=25
Participants reporting drug-related AEs (all grades)	5 (20)
Participants reporting any drug-related AEs, grades 2-5	1 (4)
Drug-related AEs	
Nausea	1 (4)
Abdominal Upset	1 (4)
Headache	1 (4)
Fatigue	2 (8)
Diarrhea	1 (4)
AEs leading to withdrawal	1 (4)
Drug-related AEs leading to withdrawal[a]	1 (4)
SAEs[b]	1 (4)

Abbreviations. AEs, adverse events; FTR, fostemsavir; CAR, current antiretroviral regimen
[a]Drug-related AEs leading to withdrawal included fatigue
[b]SAEs included chest pressure

RESULTS cont'd:

Table 3. Factors associated with CD4+T-cell changes following addition of FTR through Week 48

Characteristic	Pre-FTR CD4⁺T-cells/month 95% CI	Post-FTR CD4⁺T-cells/month 95% CI	Pre-Post Difference CD4⁺T-cells/month 95% CI
Age			
<50 years	2.14 (-0.11, 5.33)	5.80 (2.27, 9.06)*	3.66 (-1.25, 7.66)
≥50 years	1.11 (-0.23, 2.67)	2.52 (0.21, 4.78) *	1.42 (-1.59, 4.24)
Gender			
Male	1.60 (0.20, 3.50)*	4.85 (2.51, 7.07)*	3.25 (0.21, 5.88)*
Female	1.08 (-1.23, 3.38)	1.09 (-2.86, 5.05)	0.02 (-5.18, 5.22)
Race			
White	1.31 (-0.04, 2.96)	3.69 (1.40, 5.91) *	2.38 (-0.61, 5.18)
Black	1.79 (-1.01, 4.57)	3.94 (-0.20, 8.02)	2.16 (-2.92, 7.47)
Ethnicity			
Hispanic	1.50 (-0.23, 3.69)	2.64 (-0.33, 5.52)	1.14 (-2.79, 5.21)
Non-Hispanic	1.11 (-0.56, 2.76)	4.86 (2.04, 7.35) *	3.57 (0.15, 7.09)*
Baseline CD4⁺ T-cell Count			
<200 cells/mm³	0.54 (-3.63, 2.76)	3.97 (0.46, 7.29) *	3.43 (0.72, 7.58) *
≥200 cells/mm³	1.34 (0.03, 2.77)*	3.41 (1.04, 5.75) *	2.07 (-1.15, 5.22)
Anchor Drug Class			
NNRTI	0.37 (-2.94, 3.67)	2.71 (-2.25, 7.67)	2.34 (-4.03, 8.72)
PI	2.45 (0.65, 4.25) *	0.39 (-2.79, 3.58)	-2.05 (-6.44, 2.32)
INSTI	1.56 (0.00, 3.73)	4.84 (2.24, 7.29) *	3.29 (-0.10, 6.17)

*denotes a significant P-value<0.05
Abbreviations. FTR, fostemsavir; CI, confidence interval; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor

Male sex, non-Hispanic ethnicity, and baseline CD4⁺ T-cell count<200 cells/mm³ were all associated with significantly higher gains in CD4⁺ T-cell count post addition of FTR through Week 48

LIMITATIONS:

- Limitations include a small sample size and lack of randomized control group however this is a self-controlled case series in which each participant serves as their own control by contributing pre-FTR CD4⁺ T-cell parameters for comparison
- Study duration is limited to 48 weeks whereas the immune effects of FTR may extend beyond 1 year including among those who have discontinued FTR. This is relevant as data from the BRIGHTE study demonstrated increases in CD4⁺ T-cell count, CD4⁺ T-cell percentage and CD4/CD8 ratio through Week 336[4]. Further studies are needed to evaluate the durability of the immune response among FTR-treated PLWH

FUTURE DIRECTIONS:

- The RECOVER study includes a planned biomarker sub study which will include an evaluation of the impact of FTR on anti-HIV-1 T cell responses, inflammatory biomarkers, immune profiles, the proviral DNA reservoir and HIV-1 gp120. Results will be reported in future analyses
- Future analyses will also include patient-reported outcome (PRO) data on the impact of FTR on quality of life, HIV/ARV-related symptoms and treatment satisfaction

CONCLUSIONS:

- Data from the RECOVER full analysis set demonstrated significant increases in CD4⁺ T-cell counts and good tolerability after addition of FTR to baseline ARV regimens among INRs through Week 48
- At Week 48, 26% of INRs receiving FTR achieved a CD4⁺ T-cell count>350 cells/mm³, a value that has been associated with improved immune function and health-related outcomes
- No participant experienced sustained viral rebound and no changes to the baseline regimen were required to maintain viral suppression following addition of FTR
- Further studies are currently ongoing to elucidate the biological mechanisms which may mediate the impact of FTR on the immune system.

References
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