SPIRIT: Switching to Rilpivirine/Emtricitabine/Tenofovir DF Single-Tablet Regimen from Boosted Protease Inhibitor Maintains HIV-1 Suppression through Week 48

F Palella, M Fisher, P Tebas, D Shamblaw, P Ruane, J Flamm, H Wang, D Porter, S De-Oertel, T Fralich, M Bernstein, S Bush

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GILEAD
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Tel: (650) 574-3000
Fax: (650) 522-5557
Staci.Bush@gilead.com

Background

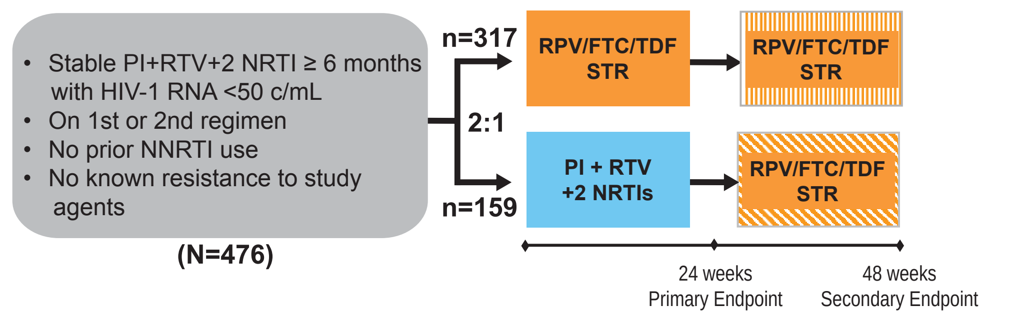
- Regimen simplification
  - improves quality of life[1-3]
  - increases long-term adherence[1-3]
  - reduces virologic failure (VF)[1-3]
  - reduces long-term toxicities[1-3]
  - increased patient satisfaction[2]
- RPV/FTC/TDF is a well-tolerated, once daily single tablet regimen (STR) treatment option[4]
- This is the first study to evaluate the safety and efficacy of switching from ritonavir-boosted protease inhibitor (PI+RTV)-based HAART to a simplified regimen of the STR RPV/FTC/TDF in virologically suppressed patients

1. Claxton AJ, et al. Clin Ther. 2001;23(8): 1296-1310
2. Stone VE, et al. J Acquir Immune Defic Syndr. 2004;36(3)
3. DHHS Guidelines. February 12, 2013
4. COMPLERA®. US Prescribing Information 01/2013. Gilead Sciences, Inc.

Methods

Figure 1. Study Design

Switching PI to Rilpivirine In-combination with Truvada as a single-tablet regimen
Multicenter, international, randomized, open-label, Phase 3b, 48-week study


Stable PI+RTV+2 NRTI ≥ 6 months with HIV-1 RNA <50 c/mL
On 1st or 2nd regimen
No prior NNRTI use
No known resistance to study agents
(N=476)
n=317
2:1
n=159
RPV/FTC/TDF STR
RPV/FTC/TDF STR
PI + RTV +2 NRTIs
RPV/FTC/TDF STR
24 weeks
Primary Endpoint
48 weeks
Secondary Endpoint

Primary Endpoint: Non-inferiority (12% margin) of RPV/FTC/TDF to PI+RTV+2 NRTIs by FDA snapshot analysis HIV-1 RNA <50 copies/mL at 24 weeks

Secondary Endpoints: Proportion of subjects on RPV/FTC/TDF who have HIV-1 RNA <50 copies/mL at Week 48
Change in fasting lipid parameters and CD4 cell count at 24 and 48 weeks
Safety and tolerability to PI+RTV+2NRTIs at 24 and 48 weeks
Patient Reported Outcomes

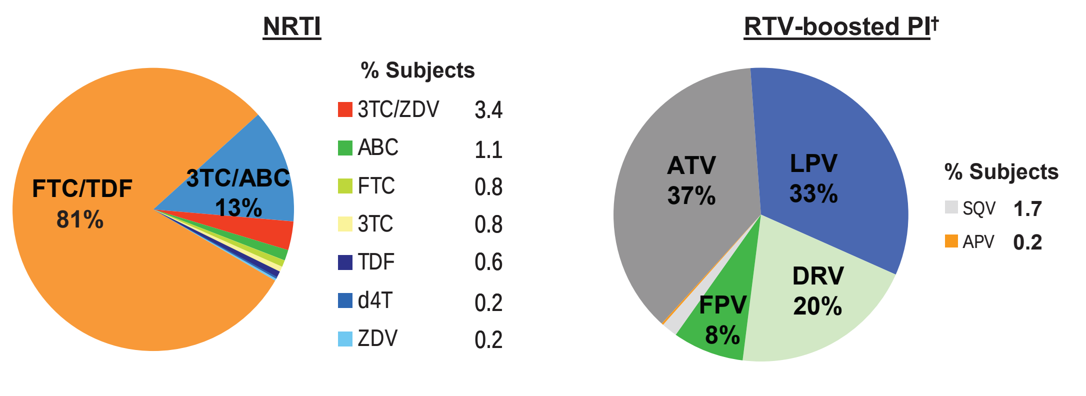
Results

Table 1. Baseline Characteristics

Characteristic	RPV/FTC/TDF N = 317	PI+RTV+2NRTIs N = 159
Median age, years (IQR)	42 (35, 48)	43 (36, 49)
Male	86%	91%
White race	76%	78%
Black race	19%	14%
Latino ethnicity	16%	20%
Median time since first ART, years (IQR)	2.9 (1.9, 4.4)	2.6 (1.7, 4.8)
Mean CD4 cell count, cells/mm³ (SD)	576 (237)	600 (259)

Results (cont'd)

Figure 2. Antiretroviral Therapy at Screening

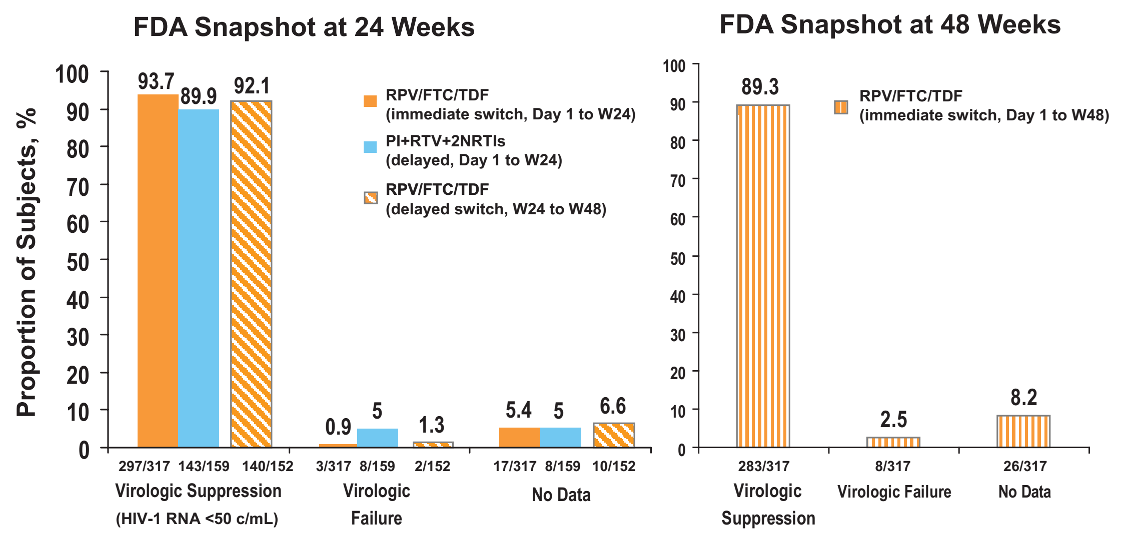


3TC, lamivudine; d4T, stavudine; ABC, abacavir; APV, amprenavir; ATV, atazanavir; DRV, darunavir; FPV, fosamprenavir; FTC, emtricitabine; LPV, lopinavir; RTV, ritonarvir; SQV, saquinavir; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine

† Includes all treated participants. 2 subjects enrolled on EFV/FTC/TDF instead of a boosted PI (protocol violation)

Figure 3. Virologic Suppression at Weeks 24 and 48 FDA Snapshot Analysis

Switching to RPV/FTC/TDF was non-inferior to remaining on PI+RTV+2NRTIs for 24 wks
Similar rates of virologic suppression were also seen at 48 wks with RPV/FTC/TDF


FDA Snapshot at 24 Weeks
Proportion of Subjects, %
93.7
89.9
92.1
0.9
5
1.3
5.4
5
6.6
297/317 143/159 140/152
3/317 8/159 2/152
17/317 8/159 10/152
Virologic Suppression (HIV-1 RNA <50 c/mL)
Virologic Failure
No Data
RPV/FTC/TDF (immediate switch, Day 1 to W24)
PI+RTV+2NRTIs (delayed, Day 1 to W24)
RPV/FTC/TDF (delayed switch, W24 to W48)
FDA Snapshot at 48 Weeks
89.3
2.5
8.2
283/317
8/317
26/317
Virologic Suppression
Virologic Failure
No Data
RPV/FTC/TDF (immediate switch, Day 1 to W48)

CD4 mean change (cells/mm³): Week 24, RPV/FTC/TDF immediate switch +20, PI+RTV+2NRTIs +32 (p=0.28), RPV/FTC/TDF delayed switch -7. Week 48, RPV/FTC/TDF immediate switch +10

Table 2. Week 24 and 48 FDA Snapshot Analysis

	RPV/FTC/TDF (Immediate, Day1 to W24) N = 317	PI+RTV+2NRTIs (Day1 to W24) N = 159	RPV/FTC/TDF (Delayed, W24 to W48) N = 152	RPV/FTC/TDF (Immediate, Day1 to W48) N = 317
Virologic Success, % HIV-1 RNA <50 copies/mL	93.7%	89.9%	92.1%	89.3%
Virologic Failure, n (%)	3 (0.9%)	8 (5.0%)	2 (1.3%)	8 (2.5%)
HIV-1 RNA ≥50 copies/mL	1	8	1	4
Discontinued due to lack of efficacy	1	0	1	2
Discontinued due to other reasons & last available HIV-1 RNA ≥50 c/mL	1	0	0	2
No Virologic Data, n (%)	17 (5.4%)	8 (5.0%)	10 (6.6%)	26 (8.2%)
Discontinued due to AE	6	0	5	7
Discontinued due to other reasons & last available HIV-1 RNA <50 c/mL	11	5	3	16
Missing data during window but on study drug	0	5	2	3

Table 3. RPV/FTC/TDF NNRTI and NRTI Resistance Through Week 48

	RPV/FTC/TDF All Subjects* N = 469
Subjects Analyzed for Resistance†, n (% study arm)	7 (1.5%)
Subjects with Resistance to ARV Regimen, n (% study arm)	4 (0.9%)
Emergent NNRTI and NRTI Resistance Mutations by Subject	Subject 1‡: K103N+L100I+M184I Subject 2: M184I Subject 3: E138E/K+M184M/I/V Subject 4: E138K+V108V/I+M184V

One subject in the PI+RTV+2NRTI arm developed resistance prior to switch at Week 24 (M184V+K70E/K)
There were no subjects with detected resistance after delayed switch to RPV/FTC/TDF

Resistance development was infrequent (<1% RPV/FTC/TDF-treated subjects)

* Includes Day 1 to Week 48 data on immediate switch arm and Week 24 to Week 48 data on delayed switch arm
† Subjects who experienced virologic rebound (two consecutive visits with HIV-1 RNA ≥400 c/mL) or had HIV-1 RNA ≥400 c/mL at last visit
‡ History of efavirenz use

Table 4. Treatment Response Among RPV/FTC/TDF-Treated Subjects with Pre-Existing K103N

	RPV/FTC/TDF (Immediate, D1 to W24) N = 317	RPV/FTC/TDF (Delayed, W24 to W48) N = 152	RPV/FTC/TDF (Immediate, D1 to W48) N = 317	RPV/FTC/TDF (Total, D1 to W48) N = 469
Subjects with Pre-existing K103N, n	18	6	18	24
Snapshot Outcome, n				
Virologic Suppression	18	5	17	22
Virologic Failure	0	0	1[a]	1[a]
No Data in Window	0	1[b]	0	1[b]

[a] Failed with resistance, pre-existing K103N and V179I and acquired M184V, E138K, and V108V/I while on study drug
[b] Missing data during window but on study drug, suppressed at prior visit

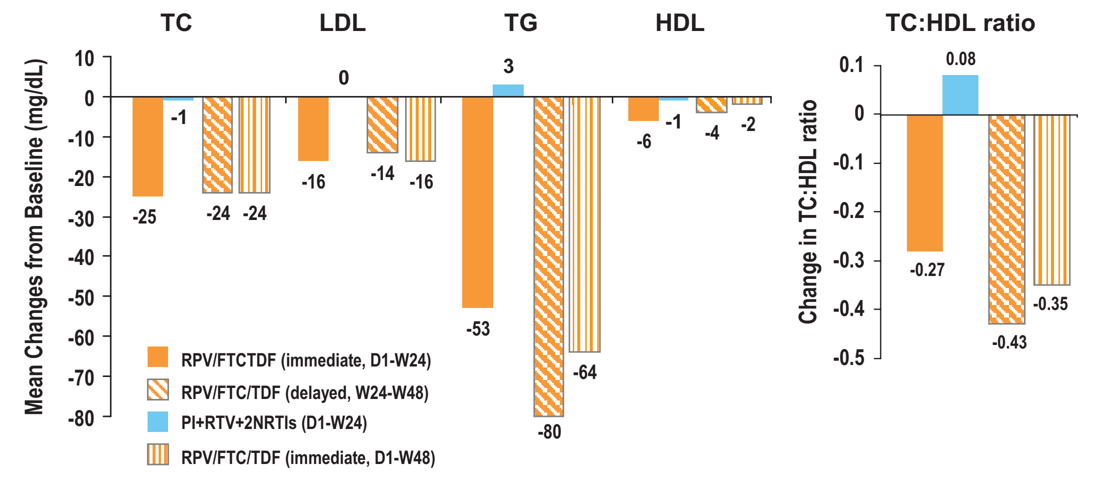
RPV/FTC/TDF-treated subjects with pre-existing K103N had a high response rate

Table 5. Grade 3 or 4 Adverse Events and Laboratory Abnormalities

	RPV/FTC/TDF N = 317 (Immediate switch, at W48)	PI+RTV+2NRTIs N = 159 (at W24)	RPV/FTC/TDF N = 152 (Delayed switch, at W24)
Grade 3 or 4 Adverse Events	18 (5.7%)	11 (6.9%)	12* (7.9%)
Grade 3 or 4 Laboratory Abnormalities	28† (8.8%)	18‡ (11.3%)	23§ (15.2%)

Adverse events and laboratory abnormalities occurring in ≥1% of subjects: * creatine kinase increase; † ALT, AST, creatine kinase, hematuria; ‡ AST, bilirubin, creatine kinase, triglycerides; § ALT, AST, creatine kinase, glycosuria

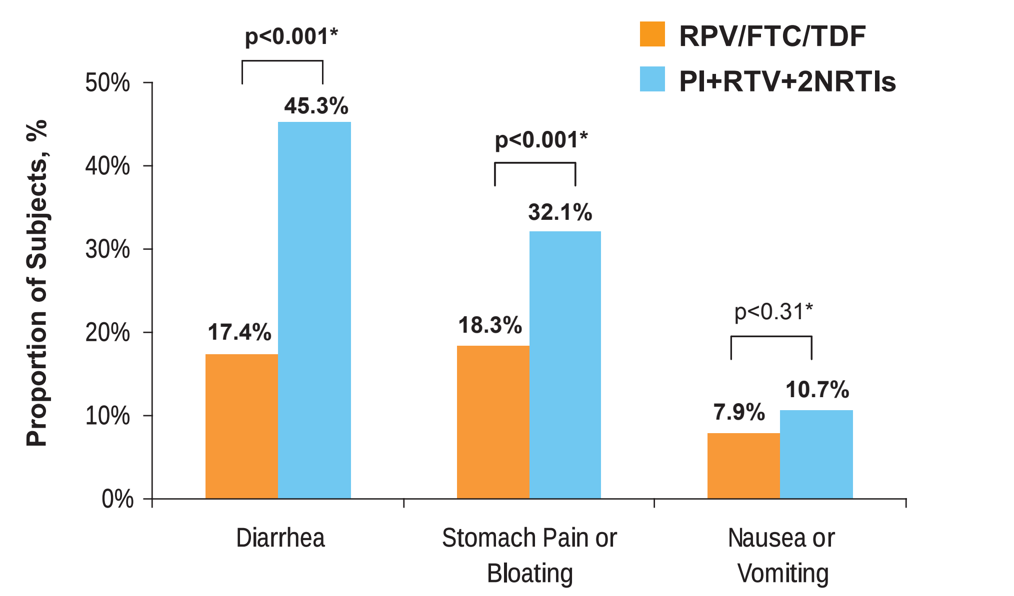
Figure 4. Changes from Baseline in Fasting Lipids



Switching to RPV/FTC/TDF resulted in improvement in fasting lipids, including TC, LDL, TGs, and TC:HDL ratio at Weeks 24 and maintained through Week 48

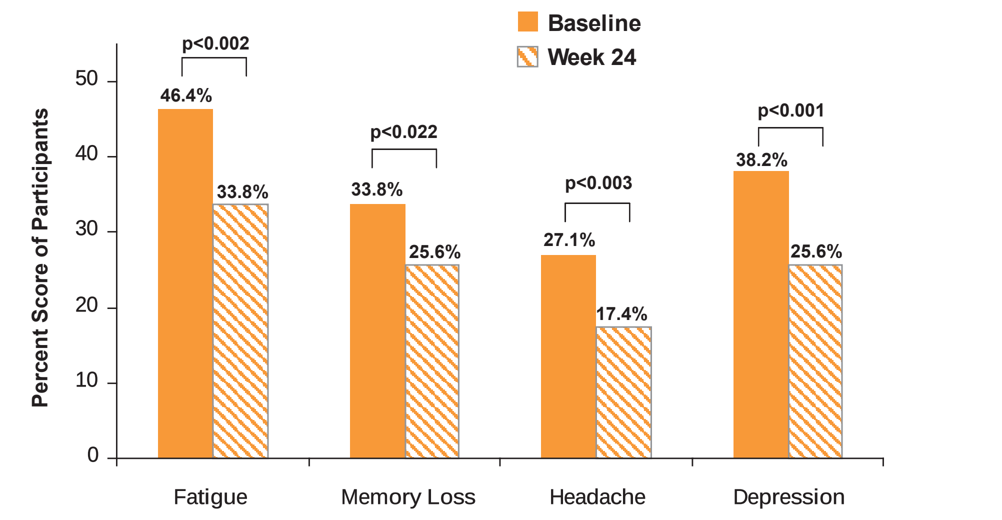
TC - total cholesterol, LDL - low-density lipoprotein, TG - triglycerides, HDL - high-density lipoprotein

Figure 5. Patient Reported Outcomes at Week 24 per HIV Symptom Index

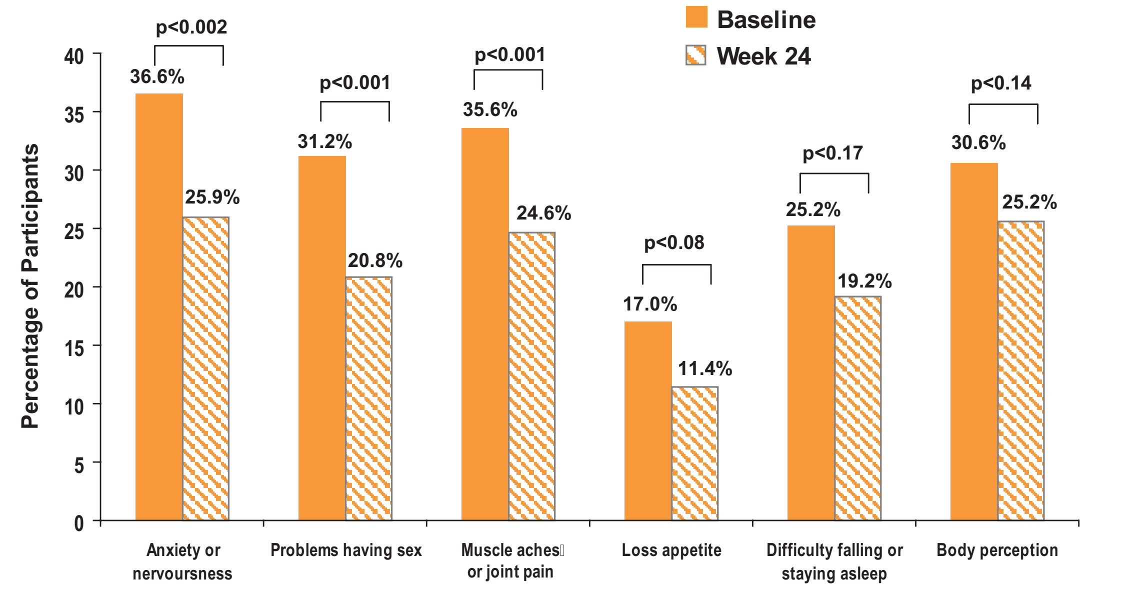


* p-value for comparison between treatment groups at Week 24 using Chi-square
Tebas P, et al. LIPO 2012; Washington, DC. #018

Improvements per Patient Report for RPV/FTC/TDF Subjects Baseline to Week 24



p-value for comparison to baseline within each treatment group is from the McNemar test


Baseline
Week 24
Percentage of Participants
p<0.002
36.6%
25.9%
p<0.001
31.2%
20.8%
p<0.001
35.6%
24.6%
p<0.08
17.0%
11.4%
p<0.17
25.2%
19.2%
p<0.14
30.6%
25.2%
Anxiety or nervousness
Problems having sex
Muscle aches or joint pain
Loss appetite
Difficulty falling or staying asleep
Body perception

p-value for comparison to baseline within each treatment group is from the McNemar test

Table 6. HIV Treatment Satisfaction Questionnaire at Week 24

Questions
How satisfied were you with your current treatment?
How well controlled do you feel your HIV has been recently?
How satisfied are you with any side effects of your present treatment?
How satisfied are you with the demands made by your present treatment?
How convenient have you been finding your treatment to be recently?
How flexible have you been finding your treatment to be recently?
How satisfied were you with your understanding of your HIV?
How satisfied are you with the extent to which the treatment fits into your lifestyle?
Would you recommend your present treatment to someone else with HIV?
How satisfied would you be to continue with your present form of treatment?

Subjects that switched to RPV/FTC/TDF reported higher satisfaction with their treatment regimen by HIV-TSQ than those who stayed on PI+RTV+2NRTIs (p<0.001§)

§ p-value for comparison between treatment groups at Week 24 from ANCOVA
HIV TSQ: HIV Treatment Satisfaction Questionnaire

Conclusions

- Through 24 weeks, switching to RPV/FTC/TDF was non-inferior to remaining on PI+RTV+2NRTIs (93.7% versus 89.9%)
  - In the delayed switch arm, virologic suppression was maintained through 24 weeks with RPV/FTC/TDF (92.1%)
  - In the immediate switch arm, virologic suppression was maintained through 48 weeks after switching to RPV/FTC/TDF (89.3%)
- Lower rate of virologic failure observed in subjects switching to RPV/FTC/TDF (0.9%) compared to remaining on PI+RTV+2NRTIs (5.0%) at Week 24
  - Low rate of virologic failure (1.3%) was also seen in the delayed switch arm
  - Through 48 weeks, RPV/FTC/TDF maintained a low rate (2.5%) of virologic failure
- Resistance development was infrequent with switching to RPV/FTC/TDF
- Switching to RPV/FTC/TDF resulted in improvement in fasting lipids, including TC, LDL, TGs, and TC:HDL ratio at Week 24 and is maintained through Week 48
- Switching to RPV/FTC/TDF led to improvement in symptoms by the HIV Symptom Index
- Higher self-reported satisfaction with their treatment regimen by the HIV-TSQ

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AUSTRIA
Greil, Richard
Haas, Bernhard
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Schalk, Horst
Vetter, Norbert

BELGIUM
Clumeck, Nathan
Vandekerckhove, Linos
Van Wijngaerden, Eric

CANADA
Brunetta, Jason
Conway, Brian
Kasper, Ken
Laplante, Francois
Rachlis, Anita

FRANCE
Cotte, Laurent
Durant, Jacques
Girard, Pierre Marie
Katlama, Christine
Molina, Jean-Michel
Pellegrin, Jean-Luc
Raffi, Francois
Slama, Laurence
Yeni, Patrcik

GERMANY
Arasteh, Keikawus
Fatkenheuer, Gerd
Knecht, Gabriele
Mauss, Stefen
Rockstroh, Jurgen
Stellbrink, Hans-Jurgen
van Lunzen, Jan

ITALY
Antinori, Andrea
D'Arminio Monforte, Antonella
Lazzarin, Adriano
Maggiolo, Franco
Rizzardini, Giuliano

SPAIN
Berenguer, Juan
Clotet, Bonaventura
Gatell, Josep Maria
Moreno, Santiago

UNITED KINGDOM
Fisher, Martin
Gazzard, Brian
Johnson, Margaret
Orkin, Chloe
Reeves, Iain
Wilkins, Edmund

UNITED STATES
Albrecht, Helmut
Bellos, Nicholaos
Benson, Paul
Berger, Daniel
Bolan, Robert
Brachman, Philip
Bredeek, Fritz
Brinson, Cynthia
Burack, Jeffery
Casanas, Beata
Cimoch, Paul
Cohen, Calvin
Crofoot, Gordon
Cruickshank, Frederick
DeJesus, Edwin
Dietz, Craig
Dretler, Robin
Edelstein, Howard
Flamm, Jason
Follansbee, Stephen
Gallant, Joel
Garcia, Fernando
Gathe, Joseph
Georgescu, Georgiana
Greiger-Zanlungo, Paola
Henry, W Keith
Horton, James
Hsu, Ricky
Jefferson, Thomas T
Johnson, Marc
Jordan, Wilbert
Khanlou, Homayoon
Kinder, Ford
Klein, Daniel
Lamarca, Anthony
Lubelchek, Ronald
Lucasti, Christopher
Markowitz, Martin
Martorell, Claudia
Mayer, Cynthia
McCurdy, Lewis
McDonald, Cheryl
McGowan, Joseph
Mildvan, Donna
Mills, Anthony
Morales Ramirez, Javier
Mounzer, Karam
Palella, Frank
Pollard, Richard
Prelutsky, David
Ramgopal, Moti
Rashbaum, Bruce
Richmond, Gary
Robbins, William
Rodriguez, Jorge
Rodwick, Barry
Ruane, Peter
Saag, Michael
Santiago, Steven
Sax, Paul
Scarsella, Anthony
Schneider, Stefan
Schrader, Shannon
Shalit, Peter
Shamblaw, David
Slim, Jihad
Tebas, Pablo
Thompson, Melanie
Towner, William
Vanig, Thanes
Wade, Barbara
Ward, Douglas
Wheeler, David
Wilkin, Aimee
Wohlfeiler, Michael
Zolopa, Andrew

SPIRIT Study Team
Chung, Devon
Das Wadhwani, Babi
Da Costa, Marilyn
Nicolellis, Amy

COMPLERA Project Team
Kozub, Benjamin
Saba, Dina
Lin, Helen
Watt, Jennifer
Kinzler, Ken
White, Kirsten
Lai, Mae
Chuck, Susan