HIV-1/HCV Coinfection Treatment with Single-Tablet Antiviral Regimens (CoSTARs): 12 Weeks of Ledipasvir/Sofosbuvir (LDV/SOF) after Randomized Switch to Elvitegravir/ Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) or Rilpivirine/F/TAF (R/F/TAF)

M Ramgopal[1], M Jain[2], F Hinestrosa[3], D Asmuth[4], G Huhn[5], J Slim[6], D Goldstein[7], J Ryu[8], S Jiang[8], M Das[8], D Piontkowsky[8], L Rossaro[8], Ning Li[9], D McColl[10] and R Haubrich[8]

[1]Midway Research Center, Fort Pierce, FL, USA, [2]University of Texas Southwestern Medical Center, Dallas, TX, USA, [3]Orlando Immunology Center, Orlando, FL, USA, [4]University of California Davis, Sacramento, CA, USA, [5]Ruth M Rothstein CORE Center, Chicago, IL, USA, [6]Saint Michael's Medical Center, Newark, NJ, USA, [7]Whitman-Walker Health, Washington DC, USA, [8]Gilead Sciences, Foster City, CA, USA, [9]Gilead Sciences, Shanghai, China, [10]Gilead Sciences, Hong Kong

7th Asian Conference on Hepatitis and AIDS
June 9-10, 2018, Beijing, China
Oral Presentation, Abstract #2.
Presentation Date/Time: Sunday June 10th, 2.45 pm

Background and Rationale

- Treatment of HCV in patients co-infected with HIV should be the same as for HCV mono-infected patients after considering drug-drug interactions.
  - Fixed-dose ledispasvir/sofosbuvir (LDV/SOF) daily for a 12 week duration is a recommended treatment for genotype 1 and 4 patients in HIV/HCV coinfection (rating 1A)[1]
- No treatment outcome data are available for concomitant HCV treatment with LDV/SOF and elvitegravir/cobicistat (E/C) or rilpivirine (R) with emtricitabine/tenofovir alafenamide (F/TAF).
- Changes in LDV, SOF, GS-331007 (major circulating SOF metabolite) and antiretroviral concentrations should not affect the efficacy or safety of HCV treatment in patients on E/C/F/TAF or R/F/TAF.
- Data on safety, tolerability and efficacy of F/TAF-based regimens with LDV/SOF are important to guide treatment decisions.

Ramgopal et al., AASLD The Liver Meeting. Oct 20-24, 2017. Washington, DC. Poster LB-12. Huhn et al., European AIDS Conference. Oct. 25-27, 2017. Milan, Italy. Poster PE16/52.

Impact of TAF Regimens on LDV/SOF Pharmacokinetics

	Victim	AUC	C_{max}	C_{tau}
R/F/TAF	SOF/GS-331007/LDV	↔	↔	↔

	Victim	AUC	C_{max}	C_{tau}
E/C/F/TAF	SOF	↑47%	↑28%	NA
	GS-331007	↑48%	↑29%	↑66%
	LDV	↑79%	↑65%	↑93%

R/F/TAF does not affect LDV, SOF and GS-331007 levels, while E/C/F/TAF can modestly increase levels of LDV, SOF and GS-331007. [2,3]

Ramgopal et al., AASLD The Liver Meeting. Oct 20-24, 2017. Washington, DC. Poster LB-12. Huhn et al., European AIDS Conference. Oct. 25-27, 2017. Milan, Italy. Poster PE16/52.

Impact of LDV/SOF on TAF Regimen Pharmacokinetics

	Victim	AUC	C_{max}	C_{tau}
LDV/SOF	RPV	↔	↔	↔
	FTC	↔	↔	↔
	TFV	↑75%	↑65%	↑85%
	TAF	↑32%	↔	↔
LDV/SOF	EVG	↔	↔	↑46%
	COBI	↑53%	↑23%	↑225%
	FTC	↔	↔	↔
	TAF	↔	↔	NA
	TFV	↔	↔	↔

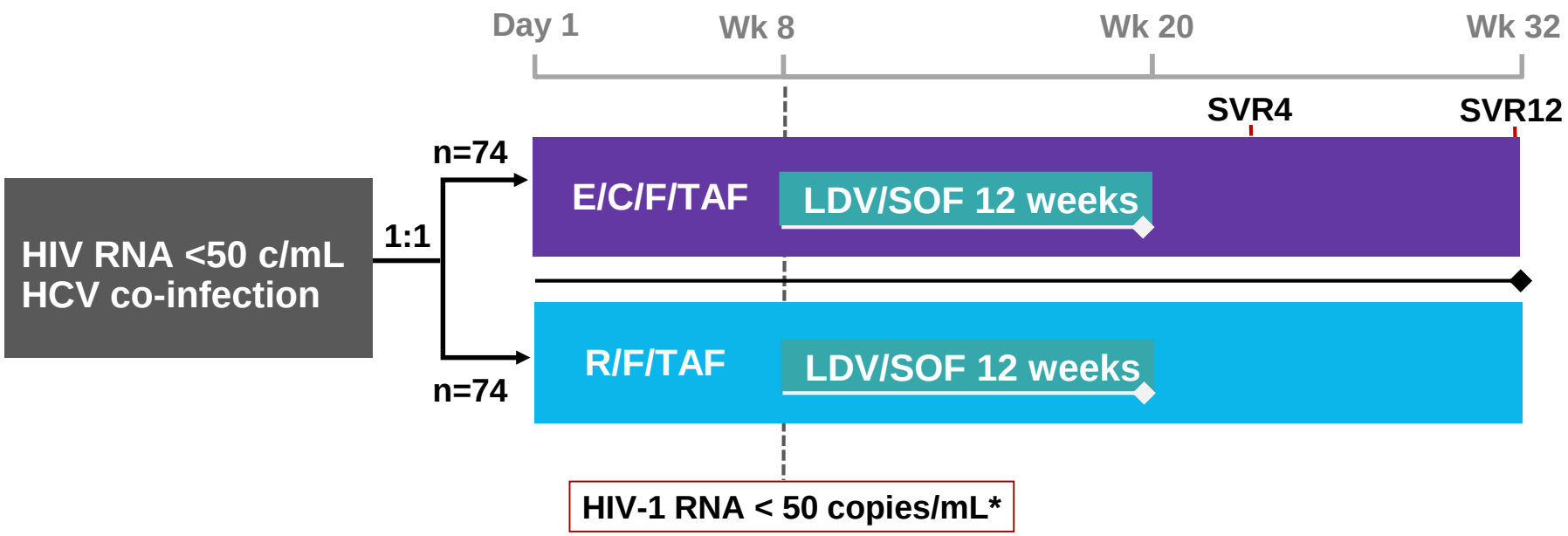
COBI, cobicistat; EVG, elvitegravir; FTC, emtricitabine; RPV, rilpivirine; TAF, tenofovir alafenamide; TFV, tenofovir.

LDV/SOF coadministered with R/F/TAF can modestly increase TFV exposures (albeit, substantially lower than TFV exposures from TDF-containing regimens); and, modestly increase COBI exposures when combined with E/C/F/TAF. [2-4]

Study Objectives

- **Primary**
  - To evaluate HCV treatment efficacy of 12 weeks of LDV/SOF as measured by SVR12
- **Secondary**
  - To determine the proportion of participants who attain SVR at 4 weeks after discontinuation of LDV/SOF (SVR4)
  - To evaluate maintenance of HIV-1 RNA suppression after switching to E/C/F/TAF or R/F/TAF at Week 24 (4 weeks after LDV/SOF treatment, by FDA snapshot algorithm)
  - To evaluate the safety and tolerability of 12 weeks of HCV treatment with LDV/SOF in HIV-1 suppressed, HCV co-infected participants switched to E/C/F/TAF or R/F/TAF
    - Adverse events during F/TAF regimen dosing alone
    - Adverse events during F/TAF regimen and LDV/SOF coadministration

Study Design



- Phase 3b, multicenter, 2-part, randomized, open-label study (NCT02707601)
- Randomization stratified by race (black vs non-black)

*Participants with HIV-1 RNA ≥ 50 copies/mL or discontinued the F/TAF-containing regimen prior to Week 8 do not qualify for LDV/SOF therapy (not assessed for HCV outcomes) and assessed only for HIV outcomes.

Endpoints and Key Inclusion/Exclusion Criteria

- **Primary endpoint**
  - Sustained virologic response (SVR; HCV RNA < LLOQ) 12 weeks after completion of LDV/SOF treatment
- **Secondary endpoints**
  - SVR4
  - HIV-1 RNA < 50 copies/mL at Week 24
  - Safety and tolerability of F/TAF-containing regimen coadministered with LDV/SOF
- **Key inclusion criteria**
  - HCV genotype 1
  - HCV treatment-naïve (± compensated cirrhosis) or treatment-experienced (non-cirrhotic)
  - Platelets ≥50,000/mm^3
  - HIV-1 RNA <50 copies/mL (≥6 months), no history of HIV virologic failure
  - Screening HIV regimens: 2 NRTIs + 3rd agent (PI, NNRTI, or INSTI)
  - No chronic HBV coinfection

LLOQ, lower limit of quantification.

Ramgopal et al., AASLD The Liver Meeting. Oct 20-24, 2017. Washington, DC. Poster LB-12. Huhn et al., European AIDS Conference. Oct. 25-27, 2017. Milan, Italy. Poster PE16/52.

Baseline Demographics and Disease Characteristics

HIV Disease Characteristics	E/C/F/TAF n=74	R/F/TAF n=74	Total N=148
Age, median years (range)	52 (26-70)	55 (25-69)	53 (25-70)
Male	78%	70%	74%
Black	41%	42%	41%
CD4 count, median cells/μL	671	640	651
$eGFR_{CG}$, median mL/min	99	100	100
Duration of prior ARV use, median years	12	16	13

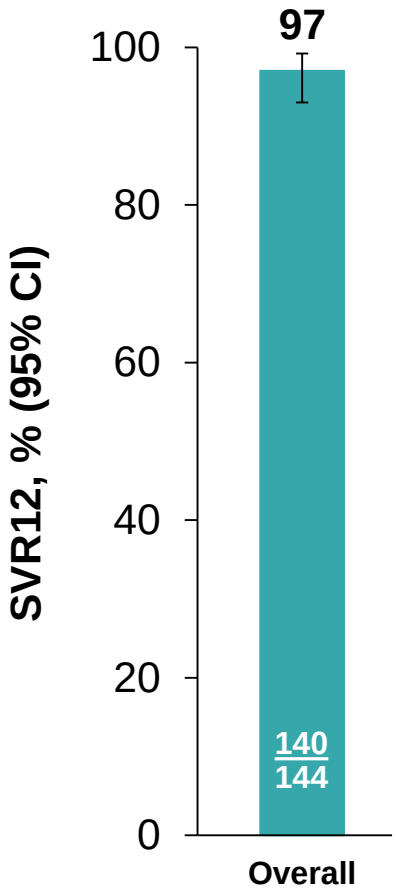
HCV Disease Characteristics	E/C/F/TAF n=72	R/F/TAF n=72	Total N=144*
HCV RNA, log_{10} IU/mL, median (range)	6.4 (1.2 - 7.3)	6.5 (4.3 - 7.5)	6.4 (1.1 - 7.5)
HCV treatment-experienced**	8%	4%	6%
ALT >1.5 x ULN	33%	32%	33%
Cirrhosis	11%	13%	12%
IL28B CC genotype	29%	22%	26%

*4 participants discontinued prior to Week 8 and were not treated with LDV/SOF.
** Prior HCV treatment included Interferon + Ribavirin ± Telaprevir. Genotype 1a and 1b: 83% and 16%.

Ramgopal et al., AASLD The Liver Meeting. Oct 20-24, 2017. Washington, DC. Poster LB-12. Huhn et al., European AIDS Conference. Oct. 25-27, 2017. Milan, Italy. Poster PE16/52.

Co-STARs: HIV-1/ HCV Treatment with LDV/SOF after Switch to E/C/F/TAF or R/F/TAF

SVR12



Ramgopal et al., AASLD The Liver Meeting. Oct 20-24, 2017. Washington, DC. Poster LB-12. Huhn et al., European AIDS Conference. Oct. 25-27, 2017. Milan, Italy. Poster PE16/52.

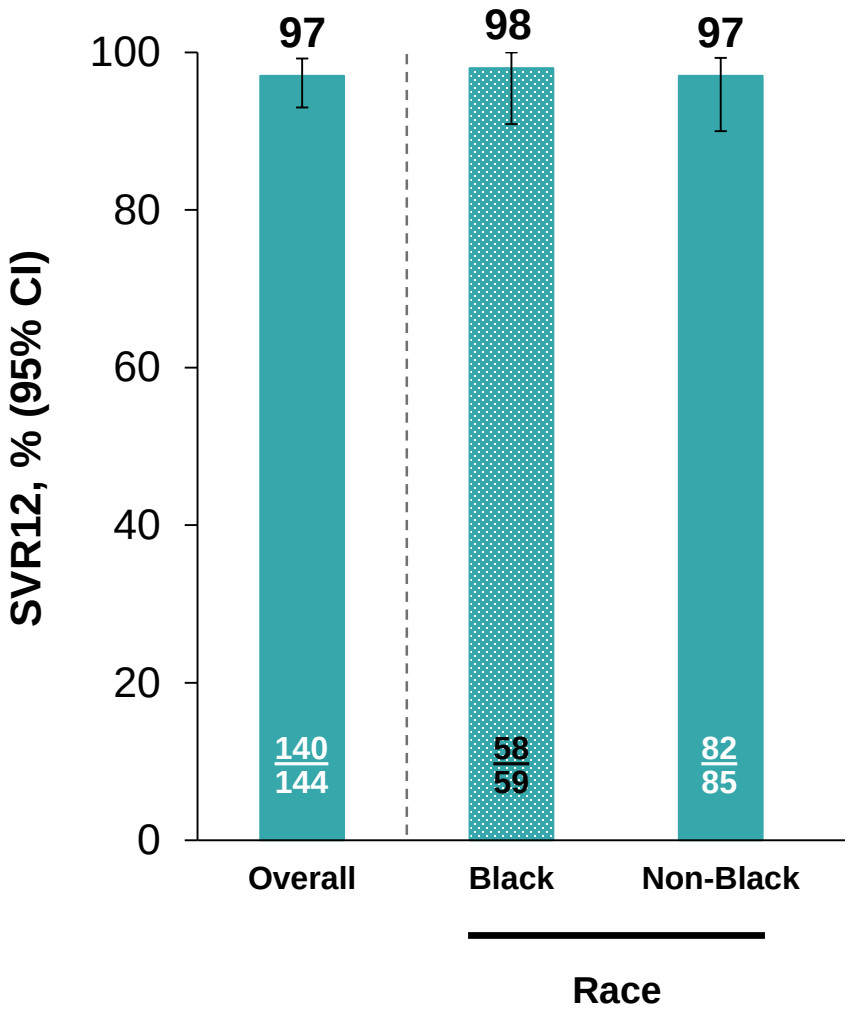
Participants Who Did Not Achieved SVR12

Participant #	SRV12 Outcome	TAF Group	Age / Sex / Race	HCV GT / IL28 GT / ±Cirrhosis	HCV Tx / BL HCVRNA LDV/SOF Adherence	Result of HCV Resistance Testing
1	**Relapse**[1]	R/F/TAF	58 yo male Pacific Islander	GT1a / CT / Cirrhotic	Naïve / 3.98 million IU/mL 100%	No NS5A/B RAS. Achieved SVR4
2	**Non-response**[2]	E/C/F/TAF	52 yo female Black	GT1a / CT / Non-cirrhotic	Naïve / 7.9 million IU/mL 92.7%	NS5A RAS: Q30R, H58D
3	**Death**[4] Missing SVR12	R/F/TAF	59 yo female American Indian	GT1a / CT / Non-cirrhotic	Naïve / 7.2 million IU/mL 52.4%	N/A HCV RNA < LLOQ at end of LDV/SOF therapy.
4	**W/D Consent**[5] Missing SVR12	R/F/TAF	46 yo female White	GT1a / TT / Non-cirrhotic	Experienced / 1.0 million IU/mL 100%	N/A Achieved SVR4

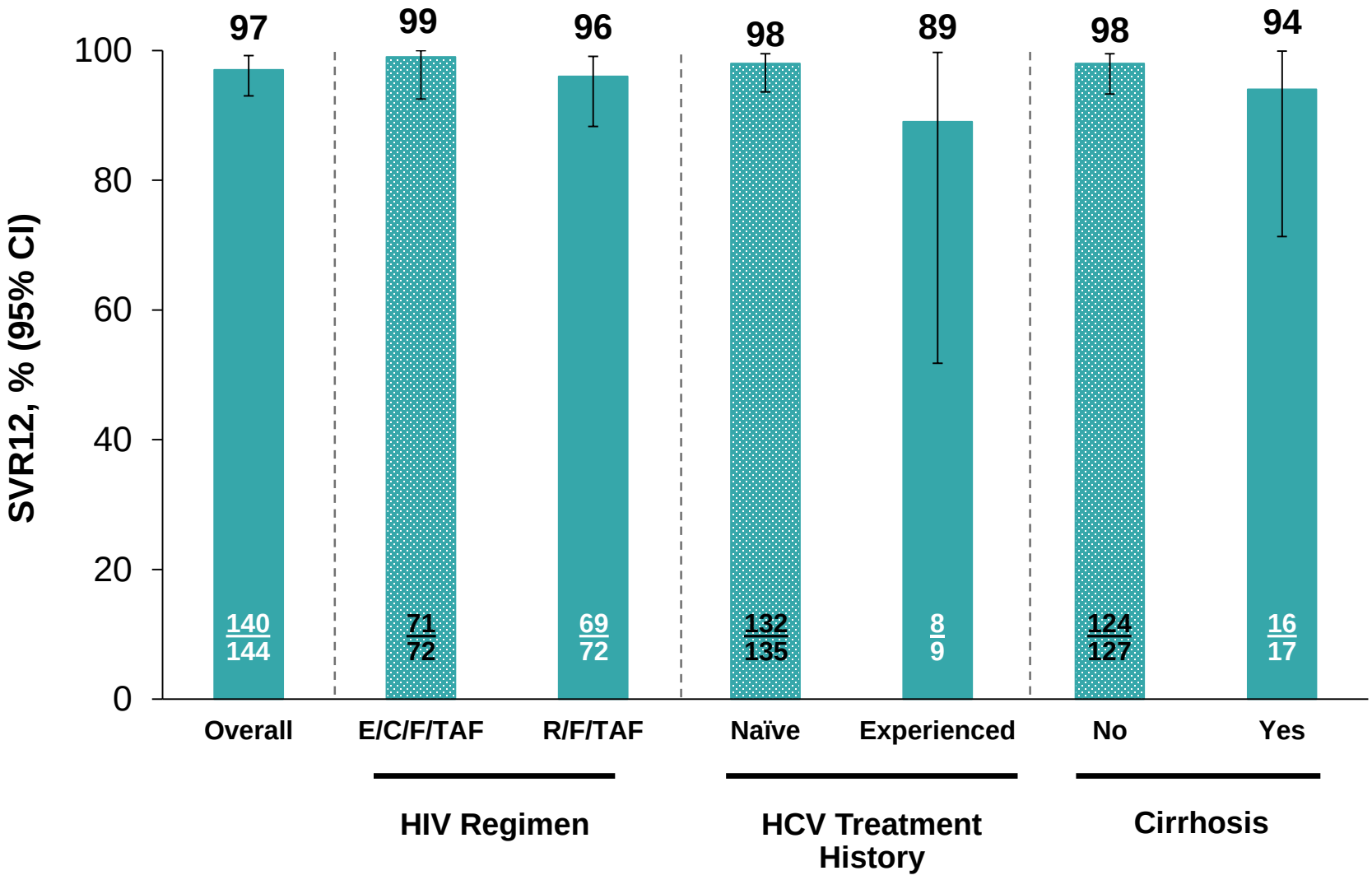
HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with lower limit of quantitation (LLOQ) at 15 IU/mL.
Relapse: Confirmed HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at last on-treatment visit.
On-treatment failure: Non-response (HCV RNA persistently ≥ LLOQ through 8 weeks of treatment).
Abbreviations: F/U=follow up. RAS, resistance-associated substitutions. Tx=treatment. W=week. W/D=withdrew. yo=year old.

1. HCV RNA at F/U-12 visit: 878,000 IU/mL. No HCV resistance testing performed at baseline. No evidence of HCV re-infection. HIV-1 RNA <50 c/mL at every study visits (baseline to end of study).
2. Total # of days treated with LDV/SOF: 76. HCV RNA (@LDV/SOF day 28): 82 IU/mL. HCV RNA (2 days after LDV/SOF d/c'd): 2,320,000 IU/mL. Retrospective testing to determine baseline NS5A resistance mutations and phylogentic testing have not been performed. HIV-1 RNA ≥ 50 copies/mL at multiple study visits. HIV-1 RNA (copies/mL) = 70 (baseline); 67 (W16); 1510 & 3070 (W24); 86 & 115 (W32).
3. Death due to metastatic carcinoma of unknown primary, between end of LDV/SOF therapy and F/U-4 visit.
4. Withdrew consent after F/U-4 visit. Participants have not returned to clinic for HCV RNA testing with treating physician.

SVR12
By Race (Black vs Non-Black)

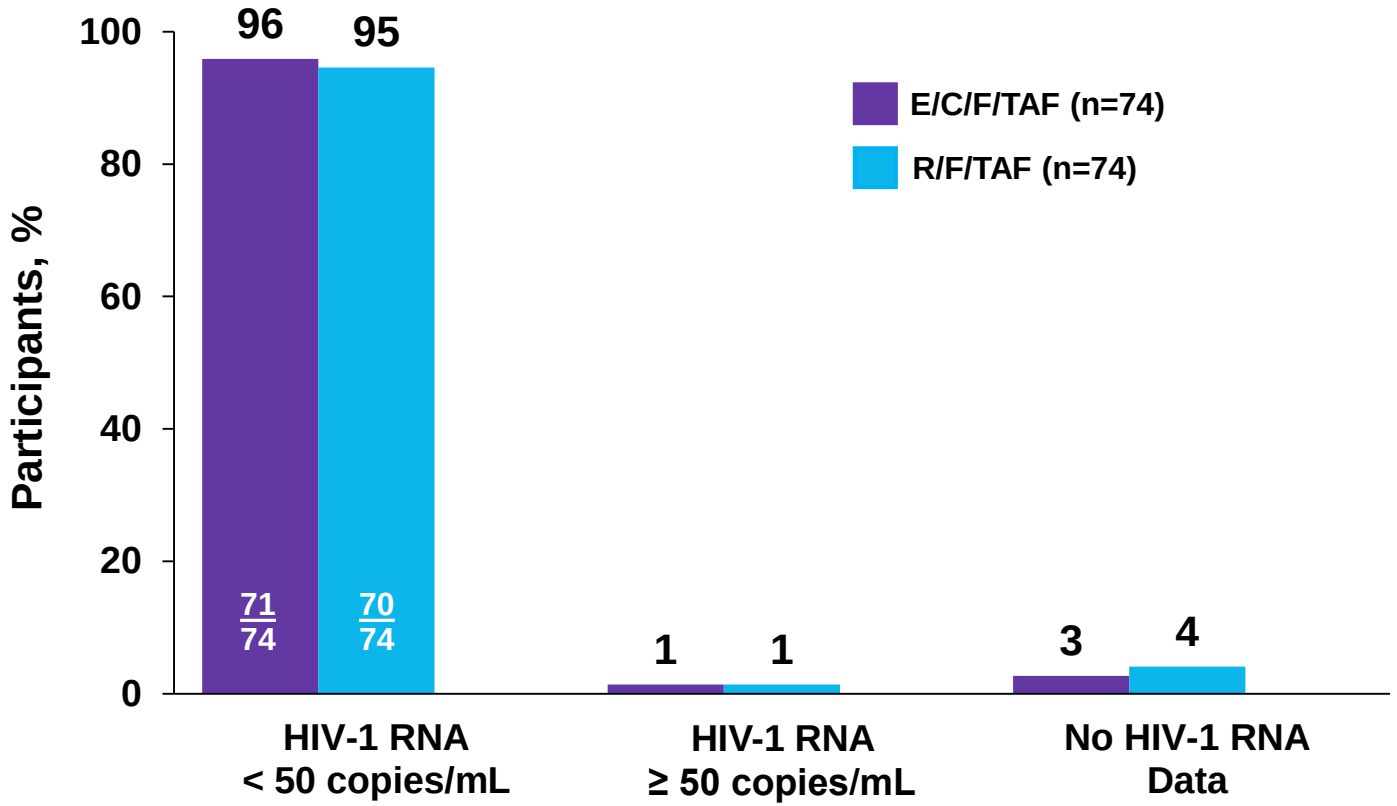


SVR12
By F/TAF Regimen, HCV Treatment History, Cirrhosis Status



Ramgopal et al., AASLD The Liver Meeting. Oct 20-24, 2017. Washington, DC. Poster LB-12. Huhn et al., European AIDS Conference. Oct. 25-27, 2017. Milan, Italy. Poster PE16/52.

HIV Virologic Outcome by FDA Snapshot Analysis 24 Weeks After Switching to E/C/F/TAF or R/F/TAF



4 participants discontinued prior to Week 8; no resistance to HIV study drugs

- 1 discontinued due to lack of efficacy (HIV-1 RNA ≥ 50 copies/mL)
- 2 discontinued due to investigator's discretion
- 1 was lost to follow-up

Change (median) from baseline in CD4 cell count (cells/µL) at Week 24:

- +16 E/C/F/TAF vs. +49 R/F/TAF (*P*=0.30)

Ramgopal et al., AASLD The Liver Meeting. Oct 20-24, 2017. Washington, DC. Poster LB-12. Huhn et al., European AIDS Conference. Oct. 25-27, 2017. Milan, Italy. Poster PE16/52.

Safety Summary
By Study Period (± LDV/SOF) vs. Whole Study

	ARVs Only	ARVs + LDV/SOF	Whole Study
	Day 1 – W8[1] n=148	W8 – W20[2] n=144	Day 1 – End[3] n=148
Any grade adverse events (AEs)	52% (77)	66% (95)	82% (121)
Grade 3 or 4 AEs	3% (5)	7% (10)	12% (17)
Serious AE	2% (3)	8% (12)	13% (19)
Discontinuation of HIV Drugs due to AEs	<1% (1)	0	<1% (1)§
Discontinuation of LDV/SOF due to AEs	N/A	0	0
Death	0	0	0.7% (1) ‡

[1]Duration: 8 weeks. [2]Duration: 12 weeks.
[3]Duration: 32 weeks (start of HIV treatment to end of both HIV and HCV treatments) + 30 days follow-up.

§One participant discontinued R/F/TAF due to worsening of pre-existing hypercholesterolemia.
‡One death due to metastatic carcinoma of unknown primary, occurred after end of LDV/SOF therapy.

The majority of clinical adverse events were mild in severity (grade 1 or 2)

ARV, antiretrovirals.

Adverse Events
By Study Period (± LDV/SOF) vs. Whole Study

	ARVs Only	ARVs + LDV/SOF	Whole Study
AEs with rates ≥ 5% (Day 1 to end of study)	**Day 1 – W8[1] n=148**	**W8 – W20[2] n=144**	**Day 1 – End[3] n=148**
Cough	5%	5%	11%
Upper Resp. Infection	3%	6%	10%
Headache	2%	8%	8%
Arthralgia	3%	6%	8%
Nausea	3%	4%	7%
Fatigue	1%	5%	6%
Diarrhea	2%	4%	6%
Abdominal pain	<1%	4%	5%

[1]Duration: 8 weeks. [2]Duration: 12 weeks.
[3]Duration: 32 weeks (start of HIV treatment to end of both HIV and HCV treatments) + 30 days follow up.
ARV, antiretrovirals.

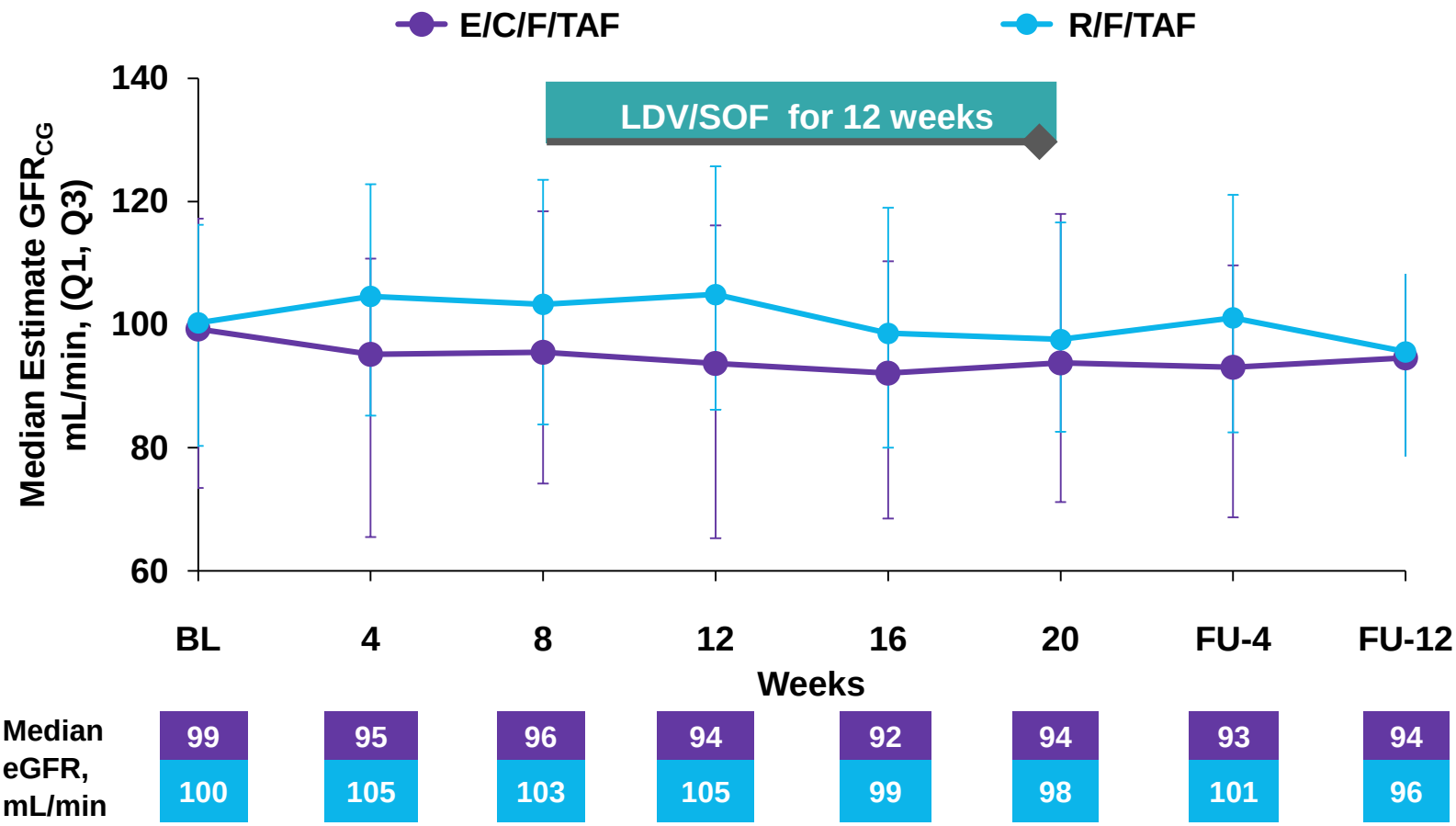
Frequency of most clinical adverse events were comparable (< 5% difference) between study periods, before and during LDV/SOF coadministration

Grade 3 or 4 Lab Abnormalities By Study Period (± LDV/SOF) vs. Whole Study

	ARVs Only	ARVs + LDV/SOF	Whole Study
Grade 3 or 4 lab abnormalities with rates ≥ 3% (Day 1 to end of study)	**Day 1 – W8[1] n=148**	**W8 – W20[2] n=144**	**Day 1 – End[3] n=148**
All grade 3 or 4 lab abnormalities	**12% (18)**	**10% (15)**	**23% (34)**
Serum glucose elevation (fasting)	3% (4)	1% (2)	4% (6)
LDL elevation	0	5% (7)	7% (10)
Hematuria (quantitative)	5% (3)	3% (3)	5% (6)
Glycosuria (urine dipstick)	2% (3)	1% (2)	3% (5)
Elevated prothrombin time	1% (2)	1% (2)	3% (5)

[1]Duration: 8 weeks. [2]Duration: 12 weeks.
[3]Duration: 32 weeks (start of HIV treatment to end of both HIV and HCV treatments) + 30 days follow up.
ARV, antiretrovirals.

Estimated GFR_{CG} Over Time by F/TAF-Containing Regimen



Summary

- High rates of SVR12 (97%) in HCV GT1 were achieved with LDV/SOF and F/TAF regimens
  - Comparable HCV efficacy with E/C/F/TAF vs. R/F/TAF coadministration
  - Comparable HCV efficacy across black and non-black subgroups
- LDV/SOF coadministered with E/C/F/TAF or R/F/TAF was well-tolerated
  - No discontinuations of HCV or HIV treatment due to clinical AEs
  - Minimal differences in clinical AEs, lab abnormalities and eGFR between E/C/F/TAF and R/F/TAF during LDV/SOF coadministration, confirming that minor differences in HIV and HCV drug exposures are not clinically meaningful
- Switch to E/C/F/TAF or R/F/TAF maintained HIV suppression in 95% of participants with no development of resistance

Conclusion

- Switching HIV regimen to E/C/F/TAF or R/F/TAF and subsequent treatment of HCV with LDV/SOF was safe, maintained HIV suppression and resulted in high rates of SVR12

Acknowledgements

- We extend our thanks to the participants, their partners and families.
- We are grateful to all GS-US-366-1992 investigators

  F Hinestrosa, M Jain, CA Kinder, C Mayer, D Asmuth, D Hagins, G Huhn, GE Crofoot, JO Morales-Ramirez, J Slim, JC Gathe, MN Ramgopal, S Applin, B Thedinger, D Goldstein, K Mounzer, K Workowski, P Cook, S Naggie, DA Wheeler, DA Wohl, D Jayaweera, M Siegel, M Wohlfeiler, C Brinson, O Osiyemi, P Tebas, P Shalit, RE Campo, T Vanig, VM Vega, WJ Fessel, A LaMarca, A Mills, DR Coulston, D Wyles, GJ Richmond, JC Bartczak, J Yozviak, K Marks, MA Thompson, M Saag, P Benson, PJ Ruane
- This study was funded by Gilead Sciences, Inc.

References

1. AASLD/IDSA Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed October 16, 2017.
2. Garrison K, Custodio J, Pang P, et al. Drug interactions between anti-HCV antivirals ledipasvir/sofosbuvir and integrase strand transfer inhibitor-based regimens. 16th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy. 2015. Washington, DC. Poster 71.
3. Custodio J, Doyle E, Pang P, et al. Lack of drug interactions between boosted and unboosted TAF-based antiretroviral single-tablet regimens (R/F/TAF and E/C/F/TAF) and the anti-HCV single-tablet regimen Ledipasvir/Sofosbuvir. ID Week. 2015. San Diego, CA. Oral 747.
4. German P, Pang P, West S, et al. Drug interactions between direct-acting anti-HCV antivirals sofosbuvir and ledipasvir and HIV antiretrovirals. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy. 2014. Washington, DC. Oral O_06.

Abbreviations

AI=American Indian. ARVs=antiretrovirals. AUC=area under the concentration-time curve. Cmax=maximal concentration. COBI=cobicistat. Ctau=trough concentration. E/C/F/TAF=elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. $eGFR_{CG}$=estimated glomerular filtration rate by Cockcroft-Gault equation. EOT=end of therapy. EVG=elvitegravir. FTC=emtricitabine. F/U=follow up. INSTI=integrase strand transfer inhibitor. LDL=low density lipoprotein. GT=gentoype. LDV=ledispasvir. NH=non-hispanic. NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=Pacific Islander. PI=protease inhibitor. Q=quartile. RAS=resistance associated substitutions. R/F/TAF=rilpivirine/emtricitabine/tenofovir alafenamide. RPV=rilpivirine. SOF=sofosbuvir. TDF=tenofovir disoproxil fumurate. Tx=treatment. W=week. W/D=withdrew. WH=White. YO=year old.