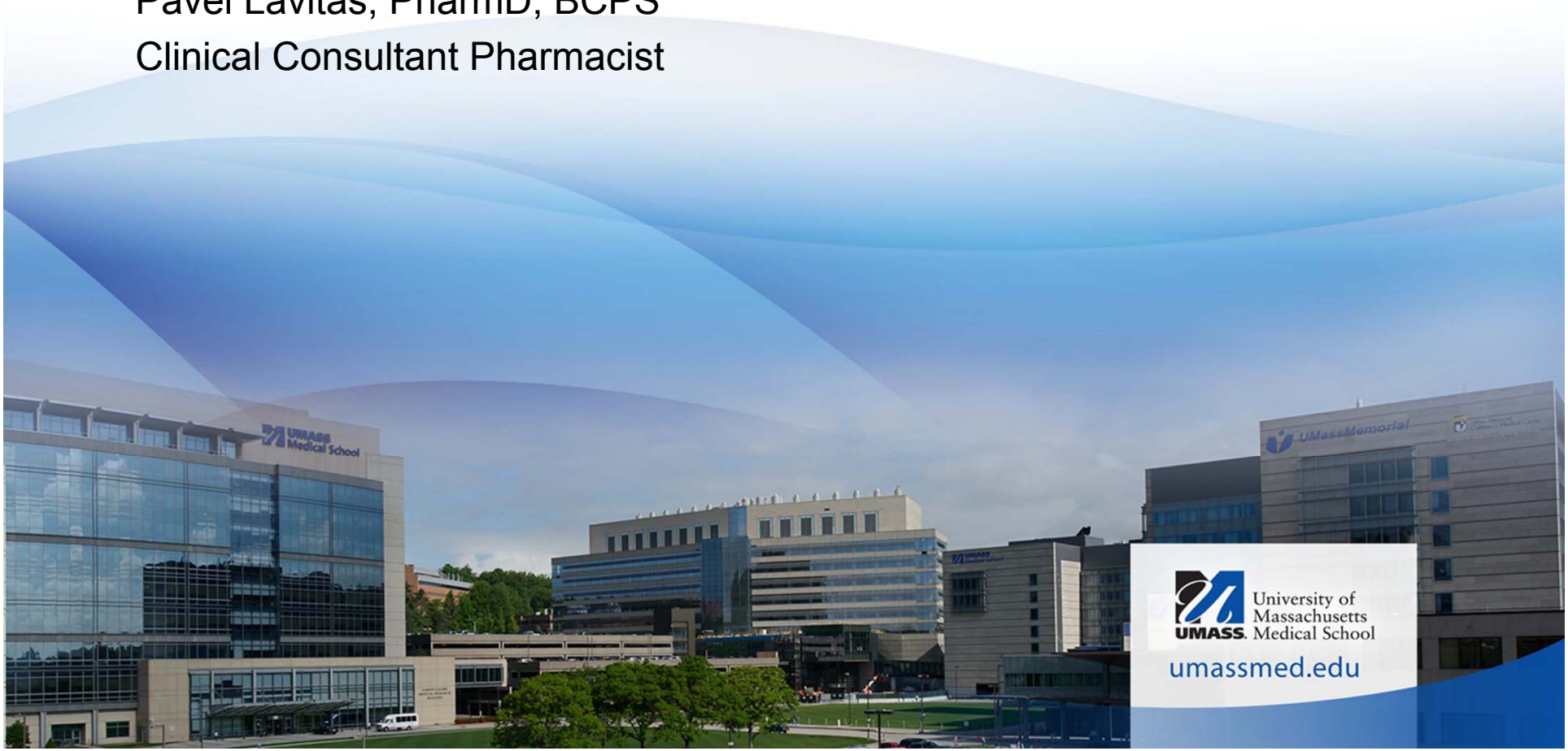
One State's Perspective on the Management of Hepatitis C Drugs

February 27, 2015

Pavel Lavitas, PharmD, BCPS
Clinical Consultant Pharmacist



Statement of Disclosure

- I have no relevant financial relationships that would be considered a conflict of interest for the purposes of this program.
- This presentation will include discussion of non-FDA approved (off-label) medication use.

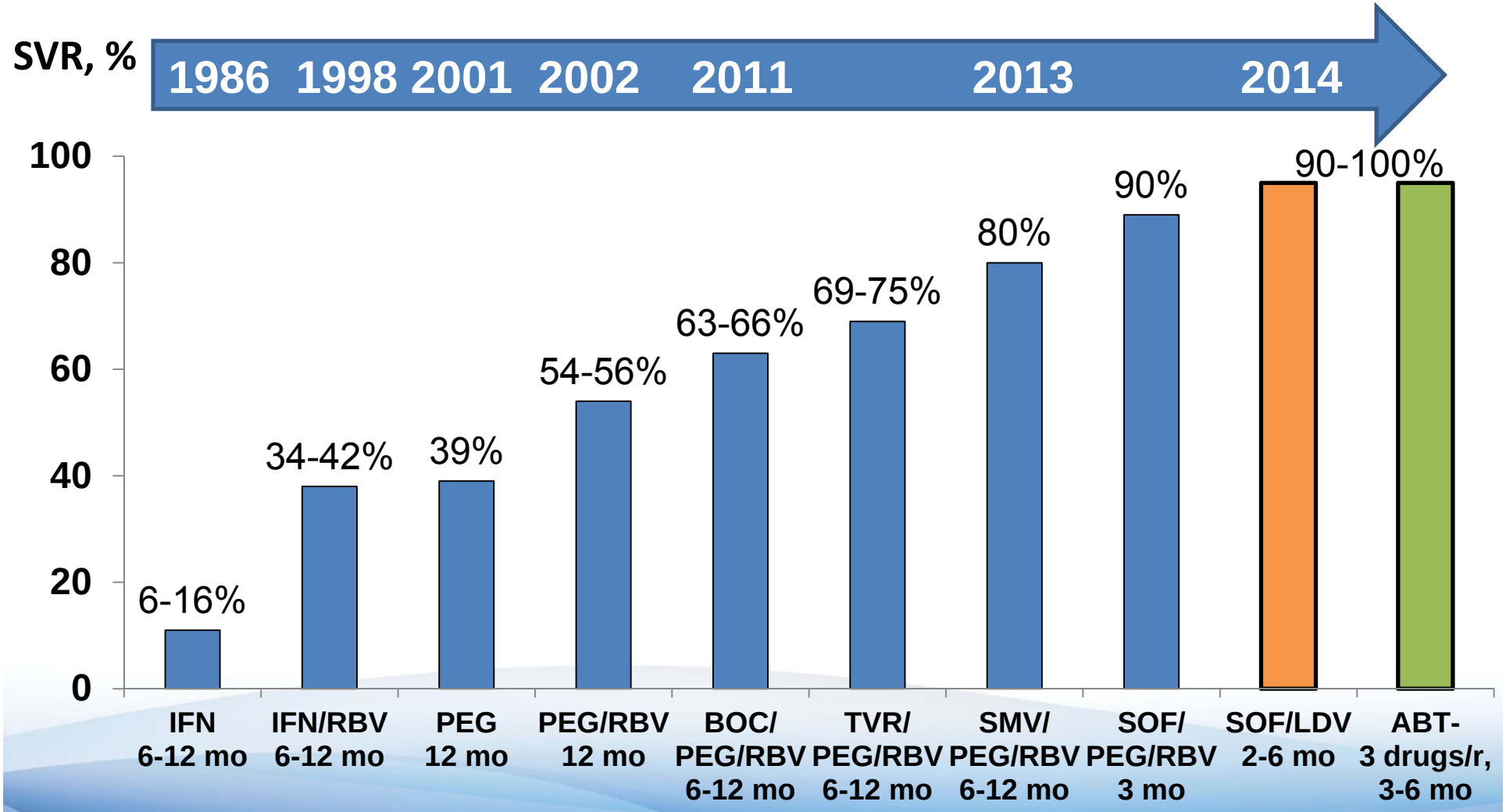
Objectives

- Describe the advances in hepatitis C treatment and drug management challenges
- Describer the hepatitis C monitoring program implemented to contain costs and to promote optimal member care
- List the outcomes of the hepatitis C monitoring program as well as the lessons learned
- Identify current management strategies for novel hepatitis C agents

Hepatitis C Overview

- Hepatitis C virus (HCV) infection is the most common chronic bloodborne infection in the United States
- At least 3.2 million people chronically infected
  - 75% are unaware they have infection
- Treatment goal is HCV eradication, preventing complications and liver related deaths
- AASLD/IDSA/IAS-USA recommend combination treatment with oral direct-acting antivirals for most patients with chronic HCV infection

Advances in the Treatment of Hepatitis C



BOC=boceprevir, IFN=interferon, LDV=ledipasvir, PEG=peginterferon alfa, RBV=ribavirin, r=ritonavir, SMV=simeprevir, SOF=sofosbuvir, SVR=sustained virologic response, TVR=telaprevir

Drug Management Challenges

- High cost of therapy ($63,000 to $300,720)
- As many as 200,000 Massachusetts residents may be infected with HCV
- Several treatment regimens are available which vary in duration, tolerability, and cost per cure
- Prioritizing members based on liver disease stage
- Suboptimal medication adherence may lead to treatment failure and drug resistance
- Medication waste if member never starts or does not complete treatment

Medication Monitoring Program Objectives

- Promote cost-effective regimen use through telephonic prescriber outreach on prior authorization (PA) requests
- Promote medication adherence through refill reminders using pharmacy claims data
- Identify members with undetectable HCV viral load 12 weeks post-therapy completion (SVR12) by conducting prescriber outreach

Monitoring Program Process Overview

Key Collaborators

- Clinical Pharmacy Services
  - Operational and clinical pharmacist
  - Pharmacy associates, supervisors, appeals
- MassHealth Office of Clinical Affairs
- Infectious Diseases specialist and Drug Utilization Review Board input
- Massachusetts Behavioral Health Partnership (MBHP)
- Prescribers and their representatives (nurses, medical assistants)
- Medicaid managed care organizations

Methods: Tracking Log

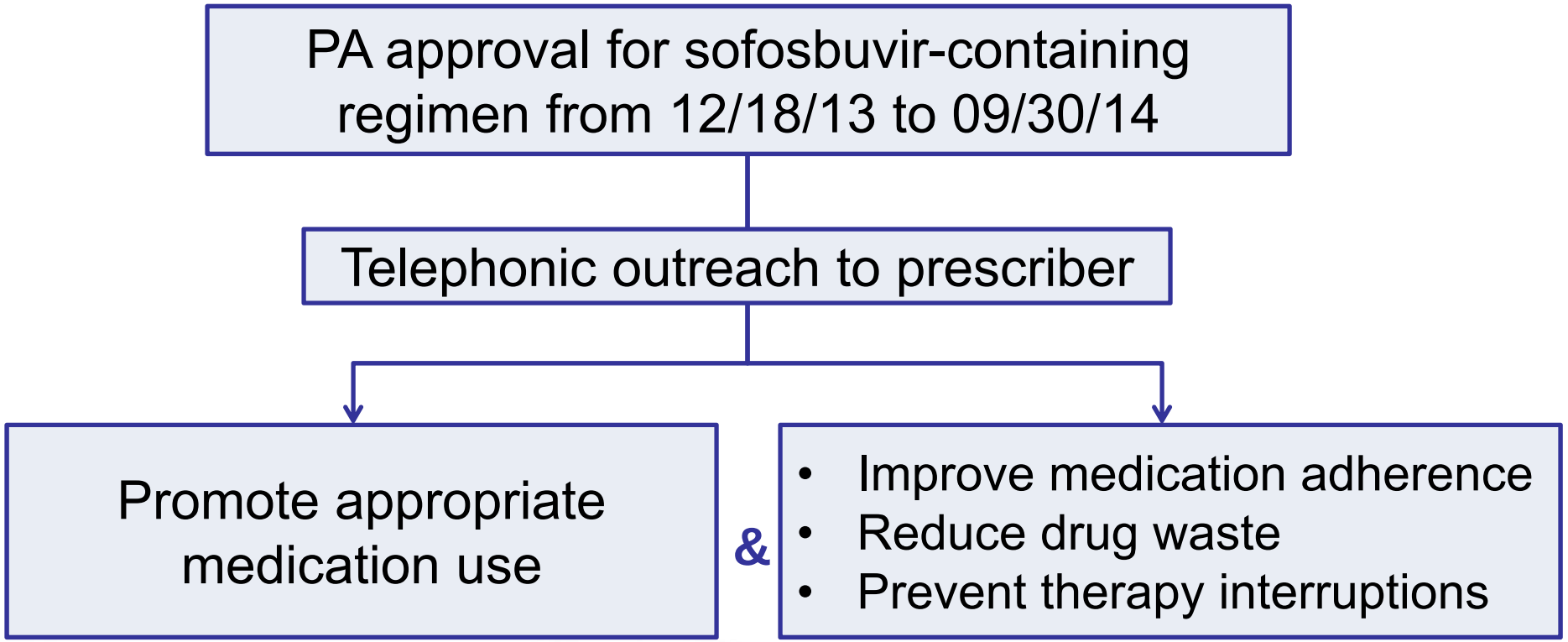
The tracking log began in December 2013

- Member and prescriber demographics
- Disease-specific parameters, such as:
  - Baseline HCV viral load
  - HCV genotype
  - Liver disease stage
  - Prior therapy with response
- Medication fill dates
- Viral load 12 weeks after treatment completion

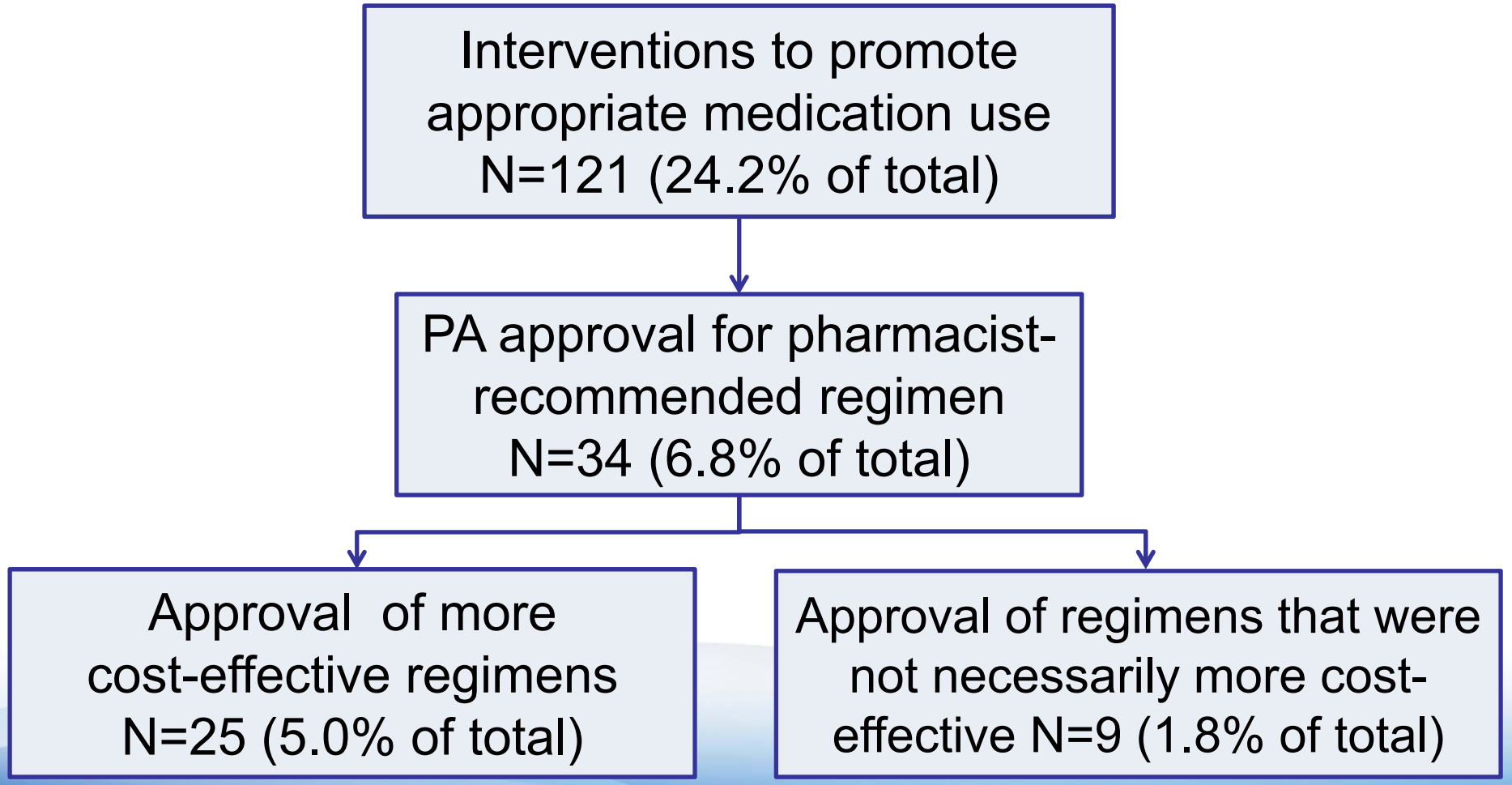
Methods: Interventions

- Clinical pharmacists contact prescriber
  - Discuss use of alternative regimens
  - Discuss appropriateness of therapy deferral
  - Close or extend PAs, if clinically appropriate
- Pharmacy associates contact prescriber
  - Inform of refill being due
  - Inquire if virological cure has been achieved
- Approved members with substance use disorders are referred to case management

Results: Study Population (N=500)



Results: Study Population (N=500)



Pharmacist Interventions: Examples

Promoting Optimal Hepatitis C Regimen Selection

February 27, 2015

University of Massachusetts Medical School
umassmed.edu

Telephonic Interventions by Pharmacists to Discuss Alternative Regimens

Cost-effectiveness considerations

- HCV genotype 1, naïve or PEG/RBV relapsers
  - SOF/RBV x 24 weeks → SOF+PEG/RBV x 12 weeks
    or SOF/SMV x 12 weeks (PEG ineligible)
- HCV genotype 2, treatment-experienced with cirrhosis
  - SOF/RBV x 12 weeks → SOF+PEG/RBV x 12 weeks
- HCV genotype 3
  - SOF/RBV x 24 weeks → SOF+PEG/RBV x 12 weeks

HCV=hepatitis C virus, PEG=peginterferon, RBV=ribavirin, SMV=simeprevir
SOF=sofosbuvir

Telephonic Interventions by Pharmacists to Discuss Alternative Regimens

Lack of efficacy data

- HCV genotype 1, prior protease inhibitor exposure
  - SOF/SMV x 12 weeks → SOF+PEG/RBV x 12 weeks

Safety concerns

- HCV genotype 1, decompensated liver disease
  - SOF/SMV x 12 weeks → SOF/RBV for up to 48 weeks

Delaying therapy consideration

- HCV genotype 1, early fibrosis (F0-F2)
  - XXXXX → SOF/LDV or 3-D combination*

HCV=hepatitis C virus, PEG=peginterferon, RBV=ribavirin, SMV=simeprevir, SOF=sofosbuvir
*ombitasvir/paritaprevir/ritonavir; dasabuvir ± RBV

Interventions Resulting in Regimen Change

HCV Genotype 1 Infection PA Approvals

Requested Regimen	Recommended Regimen	# of Members	Member Characteristics
SOF/RBV	SOF/SMV±RBV	14*	PEG ineligible
SOF+PEG/RBV	SOF/SMV	5	PEG/RBV nonresponder
SOF/SMV	SOF+PEG/RBV	4*	Treatment-naïve
SOF/RBV	SOF+PEG/RBV	2*	PEG eligible
SOF/SMV	SOF+RBV	2	Prior PI exposure and PEG ineligibility
SOF/SMV	SOF+PEG/RBV	1	Prior PI exposure
SOF/SMV	SOF+RBV	1	Liver decompensation

PEG=peginterferon alfa, PI=protease inhibitor, RBV=ribavirin, SMV=simeprevir, SOF=sofosbuvir
*A total of 19 members who completed treatment with the more cost-effective regimen were included in the cost-avoidance analysis.

Interventions Resulting in Regimen Change

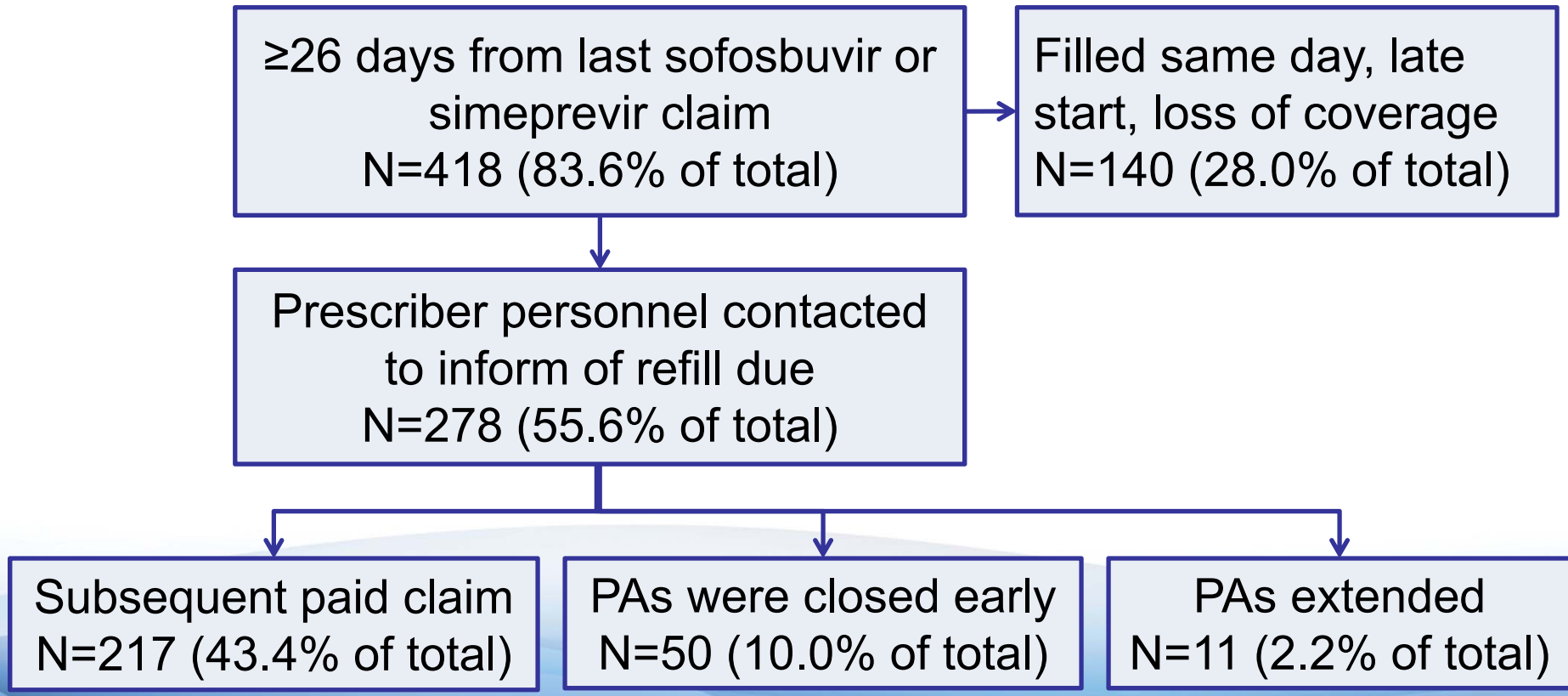
HCV Genotype 3 Infection PA Approvals			
Requested Regimen	**Recommended Regimen**	**# of Members**	**Member Characteristics**
SOF+RBV	SOF+PEG/RBV	3*	Treatment-naïve, no cirrhosis
SOF+RBV	SOF+PEG/RBV	1*	Treatment-naïve, cirrhosis
SOF+RBV	SOF+PEG/RBV	1*	Treatment-experienced, cirrhosis

PEG=peginterferon alfa, RBV=ribavirin, SOF=sofosbuvir

*A total of 19 members who completed treatment with the more cost-effective regimen were included in the cost-avoidance analysis.

Results: Study Population (N=500)

Promoting medication adherence, drug waste reduction, and preventing interruptions in therapy



Interventions to Improve Medication Adherence

Clinical Pharmacist Interventions Resulting in PA Closure				
Rationale for Intervention	**Number of Members**			
	SOF/RBV	**SOF+PEG/RBV**	**SOF/SMV±RBV**	**Total**
Therapy deferral	9	3	3	**15**
Adverse event	9	5	0	**14**
Nonadherence	7	1	2	**10**
Loss to follow-up	3	1	2	**6**
Loss of coverage	3	0	0	**3**
Change in treatment plan	1	0	1	**2**
Total	**32**	**10**	**8**	**50**

PA=prior authorization, PEG=peginterferon alfa, RBV=ribavirin, SMV=simeprevir, SOF=sofosbuvir

Interventions to Improve Medication Adherence

Clinical Pharmacist Interventions Resulting in PA Extension				
Rationale for Intervention	**Number of Members**			
	SOF/RBV	**SOF+PEG/RBV**	**SOF/SMV±RBV**	**Total**
Late start	2	5	4	**11**
Total (closed or extended PAs)	**34**	**15**	**12**	**61**

PA=prior authorization, PEG=peginterferon alfa, RBV=ribavirin, SMV=simeprevir, SOF=sofosbuvir

- **A total of 17 members with comorbid substance use disorders have been referred for enrollment into a case management program.**

Summary of Cost-Avoidance Estimates

Interventions to Promote Cost-Effective Medication Use

- 19 members completed therapy with more cost-effective, pharmacist-recommended regimen
    - Estimated cost avoidance: **$884K to $1.7M***
        - 11 members achieved SVR12
        - 3 had undetectable viral load at the end of treatment
        - 5 - data is pending

Interventions to Reduce Drug Waste

- Pharmacies for two of 51 members, for whom PAs have already been closed early, have attempted to submit a claim, which were rejected at the point-of-sale
    - Estimated drug waste cost-avoidance: **$59K**

*Cost-avoidance was calculated as the difference in cost (or cost/cure) between the pharmacist-recommended regimen and the regimen originally requested by the prescriber.

Summary

- A Hepatitis C monitoring program has proven to be successful in this Medicaid program
  - Opportunity for optimal, cost-effective regimen selection
  - Refill reminders and member referral to case management may promote medication adherence
  - Potential for drug waste reduction from identifying members who discontinue therapy
  - Ability to identify members who achieve virologic cure
- High cost of therapy, high prevalence of chronic infections, and availability of several regimens support an ongoing monitoring program

Lessons Learned

- Proactively develop a management strategy for the new agents before FDA approval
- Continuous quality improvement
  - Timely revisions to internal guidelines
  - Staff training and retraining
  - Tracking outcomes
- Cooperation at all levels
  - Operational, clinical, prescriber and pharmacy
- Serve as a resource to prescribers
  - Refill reminders outreach
  - Online materials

FDA=Food and Drug Administration

Commonwealth of Massachusetts
Executive Office of Health and Human Services
www.mass.gov/druglist

MassHealth Pharmacy Program Hepatitis C Clinical Information

The following hepatitis C therapies require prior authorization (PA).

Direct-acting Antivirals
Harvoni (ledipasvir/sofosbuvir)
Incivek (telaprevir)
Olysio (simeprevir)
Sovaldi (sofosbuvir)
Victrelis (boceprevir)
Interferon Products
Infergen (interferon-alfacon)
Pegasys (peginterferon alfa-2a)
PegIntron (peginterferon alfa-2b)
Ribavirin
Rebetol (ribavirin) capsules*
Rebetol (ribavirin) solution: in members ≥19 years old
Ribasphere (ribavirin): 200 mg capsules
Ribasphere (ribavirin): 400 mg and 600 mg tablets
Ribavirin dose pack

*Both brand and generic require a prior authorization

Note: Ribavirin 200 mg tablets do not require PA.

Hepatitis C consensus guidelines

Consensus guidelines have been developed by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) and can be accessed here: http://HCVguidelines.org.

Direct-acting antivirals

Hepatitis C virus (HCV) protease inhibitors, Incivek (telaprevir), Olysio (simeprevir), and Victrelis (boceprevir) are Food and Drug Administration (FDA)-approved for the treatment of chronic HCV genotype 1 infection, as components of antiviral treatment regimen. Incivek (telaprevir) and Victrelis (boceprevir) were the first HCV protease inhibitors available. [1-3] However, their use is no longer recommended due to high rates of serious adverse events, long treatment duration, high pill burden, drug-drug interactions, frequent dosing and monitoring, and dietary requirements.[4] Incivek (telaprevir) has been discontinued in the United States in October 2014.[5]

Sustained Virologic Response (SVR) Rates Amongst Direct-acting Antivirals in HCV Genotype 1 Subjects [1-4,6-8]

Subject Characteristics	Boceprevir*	Simeprevir*	Sofosbuvir*	Ledipasvir/ sofosbuvir	Telaprevir*
Treatment-naïve	63 to 66%	80%	89%	94 to 99%	69 to 75%
Prior relapser	69 to 75%	79%	71%†	95 to 100%	83 to 88%
Prior partial responder	40 to 52%	67%		92 to 98%	54 to 59%
Prior null responder	38%	45%			29 to 33%

*Added to peginterferon alfa and ribavirin. Direct-acting antivirals have not been directly compared in clinical trials.
†FDA estimate in treatment-experienced subjects

Sovaldi (sofosbuvir) is a once-daily, oral HCV nucleotide analog NS5B polymerase inhibitor FDA-approved for the treatment of HCV genotype 1, 2, 3 or 4 infection, including patients with hepatocellular carcinoma (HCC) awaiting liver transplantation or HCV/human immunodeficiency virus co-infection. It is indicated for use in combination with peginterferon alfa and ribavirin in the treatment of HCV genotype 1 and 4 infection and in combination with ribavirin alone in the treatment of HCV genotype 2 and 3 infection, and in patients with HCC awaiting liver transplant. Use in combination with ribavirin alone can be considered in patients with HCV genotype 1 infection who are not candidates for an interferon-based regimen.[6]

Harvoni (ledipasvir/sofosbuvir) is a once-daily combination of ledipasvir, an HCV NS5A inhibitor, and sofosbuvir, an HCV NS5B polymerase inhibitor. Both drugs interfere with the enzymes required for viral replication. Harvoni (ledipasvir/sofosbuvir) is indicated for the treatment of chronic hepatitis C genotype 1 infection in adults. The FDA-approved treatment duration is eight, 12 or 24 weeks depending on prior treatment history, cirrhosis status and baseline viral load. Eight weeks of treatment can be considered for treatment-naïve patients without cirrhosis and baseline HCV viral load < 6 million IU/mL. It is the first FDA-approved regimen that does not require administration with peginterferon alfa or ribavirin.[7]

Comparison of SVR Rates between Select Ledipasvir/Sofosbuvir Regimens in HCV Infected Subjects[7,9-12]

Subject Characteristics	Regimen*	SVR	Study Name
Treatment-naïve, no cirrhosis			
Genotype 1, HCV RNA < 6 million IU/mL	**LDV+SOF for 8 weeks**	**97% (119/123)**	**ION-3**
	LDV+SOF for 12 weeks	**96% (126/131)**	**ION-3**
Genotype 1a	**LDV+SOF for 8 weeks**	**93% (159/171)**	**ION-3**
	LDV+SOF+RBV for 8 weeks	92% (159/172)	ION-3
	LDV+SOF for 12 weeks	**95% (163/172)**	**ION-3**
Genotype 1a (84% without cirrhosis)	**LDV+SOF for 12 weeks**	**99% (141/142)**	**ION-1**
	LDV+SOF+RBV for 12 weeks	100% (143/143)	ION-1
	LDV+SOF for 24 weeks	100% (143/143)	ION-1
	LDV+SOF+RBV for 24 weeks	100% (141/141)	ION-1
Genotype 1b	**LDV+SOF for 8 weeks**	**98% (42/43)**	**ION-3**
	LDV+SOF+RBV for 8 weeks	95% (42/44)	ION-3
	LDV+SOF for 12 weeks	**98% (43/44)**	**ION-3**
Genotype 1b (84% without cirrhosis)	**LDV+SOF for 12 weeks**	**100% (66/66)**	**ION-1**
	LDV+SOF+RBV for 12 weeks	100% (67/67)	ION-1
	LDV+SOF for 24 weeks	97% (66/68)	ION-1
	LDV+SOF+RBV for 24 weeks	100% (71/71)	ION-1
Treatment-naïve, cirrhosis			
Genotype 1	**LDV+SOF for 12 weeks**	**97% (32/33)**	**ION-1**
	LDV+SOF+RBV for 12 weeks	100% (33/33)	ION-1
	LDV+SOF for 24 weeks	97% (31/32)	ION-1
	LDV+SOF+RBV for 24 weeks	100% (36/36)	ION-1
Treatment-experienced, no cirrhosis			
Genotype 1a, prior PEG/RBV±PI (80% without cirrhosis)	**LDV+SOF for 12 weeks**	**95% (82/86)**	**ION-2**
	LDV+SOF+RBV for 12 weeks	95% (84/88)	ION-2
	LDV+SOF for 24 weeks	99% (84/85)	ION-2
	LDV+SOF+RBV for 24 weeks	99% (87/88)	ION-2
Genotype 1b, prior PEG/RBV±PI (80% without cirrhosis)	**LDV+SOF for 12 weeks**	**87% (20/23)**	**ION-2**
	LDV+SOF+RBV for 12 weeks	100% (23/23)	ION-2
	LDV+SOF for 24 weeks	100% (24/24)	ION-2
	LDV+SOF+RBV for 24 weeks	100% (23/23)	ION-2
Treatment-experienced, cirrhosis			
Genotype 1, prior PEG/RBV±PI	LDV+SOF for 12 weeks	86% (19/22)	ION-2
	LDV+SOF+RBV for 12 weeks	82% (18/22)	ION-2
	LDV+SOF for 24 weeks	**100% (22/22)**	**ION-2**
	LDV+SOF+RBV for 24 weeks	100% (22/22)	ION-2
Other patient populations			
Genotype 1, Child Pugh Class B	LDV+SOF for 12 weeks	65% (13/20)	ELECTRON-2
Genotype 1, prior SOF failure	LDV+SOF+RBV for 12 weeks	100% (19/19)	
Genotype 3, (88% w/o cirrhosis)	LDV+SOF for 12 weeks	64% (16/25)	
Genotype 3, (81% w/o cirrhosis)	LDV+SOF+RBV for 12 weeks	100% (26/26)	

Comparison of SVR Rates between Select Sofosbuvir Regimens in HCV Infected Subjects[6,13-16]

Subject Characteristics	Regimen*	SVR	Study Name
HCV Genotype 1			
Treatment-naïve, no cirrhosis	**SOF+PEG/RBV for 12 weeks**	**92%**	**NEUTRINO**[†]
Treatment-naïve, cirrhosis	**SOF+PEG/RBV for 12 weeks**	**80%**	**NEUTRINO**[†]
	SOF+SMV±RBV for 12 to 24 weeks[‡]	**> 90%**	**COSMOS**
Treatment-naïve, with or without cirrhosis	**SOF+RBV for 24 weeks**	**68%**	**SPARE**
Treatment-experienced, no cirrhosis	**SOF+PEG/RBV for 12 weeks**	**71%**	**FDA estimate**
Treatment-experienced, cirrhosis	**SOF+PEG/RBV for 12 weeks**		
	SOF+SMV±RBV for 12 to 24 weeks[‡]	**>90%**	**COSMOS**
HCV Genotype 2			
Treatment-naïve, no cirrhosis	**SOF+RBV for 12 weeks**	**92 to 98%**	**POSITRON**[§]**; VALENCE; FISSION**
Treatment-naïve, cirrhosis	**SOF+RBV for 12 weeks**	**91 to 94%**	**FISSION; POSITRON**[§]
Treatment-experienced, no cirrhosis	**SOF+RBV for 12 weeks**	**91 to 96%**	**VALENCE; FUSION**
	SOF+RBV for 16 weeks	100%	FUSION
	SOF+PEG/RBV for 12 weeks	100%	LONESTAR-2
Treatment-experienced, cirrhosis	**SOF+RBV for 12 weeks**	**60 to 88%**	**FUSION; VALENCE**
	SOF+RBV for 16 weeks	78%	FUSION
	SOF+PEG/RBV for 12 weeks	93%	LONESTAR-2
HCV Genotype 3			
Treatment-naïve, no cirrhosis	SOF+RBV for 12 weeks	61 to 68%	FISSION; POSITRON[§]
	SOF+RBV for 24 weeks	**93%**	**VALENCE**
Treatment-naïve, cirrhosis	SOF+RBV for 12 weeks	21 to 34%	POSITRON[§]; FISSION
	SOF+RBV for 24 weeks	**92%**	**VALENCE**
Treatment-experienced, no cirrhosis	SOF+RBV for 12 weeks	37%	FUSION
	SOF+RBV for 16 weeks	63%	FUSION
	SOF+RBV for 24 weeks	**85%**	**VALENCE**
	SOF+PEG/RBV for 12 weeks	83%	LONESTAR-2
Treatment-experienced, cirrhosis	SOF+RBV for 12 weeks	19%	FUSION
	SOF+RBV for 16 weeks	61%	FUSION
	SOF+RBV for 24 weeks	**60%**	**VALENCE**
	SOF+PEG/RBV for 12 weeks	83%	LONESTAR-2
HCV Genotype 4			
Treatment-naïve	**SOF+PEG/RBV for 12 weeks**	**96%**	**NEUTRINO**
Treatment-experienced	**SOF+PEG/RBV for 12 weeks**	**Not studied**	
HCV Genotype 1 through 6 infected subjects with HCC awaiting liver transplant			
Treatment-naïve and treatment-experienced	**SOF+RBV for up to 48 weeks**	**64%**[‖]	**P7977-2025**
HCV Genotype 1, 2 and 3 infected subjects with human immunodeficiency virus co-infection			
Genotype 1 treatment-naïve	**SOF+RBV for 24 weeks**	**76%**	**PHOTON-1**
Genotype 2 treatment-naïve and experienced	**SOF+RBV for 12 weeks**	**88%**	**PHOTON-1**
Genotype 3 treatment-naïve and experienced	**SOF+RBV for 24 weeks**	**92%**	**PHOTON-1**

Current and Future Management Strategies

Appropriate Member Screening, Regimen Selection, Treatment Monitoring, Outcome Collection

February 27, 2015

University of Massachusetts Medical School
umassmed.edu

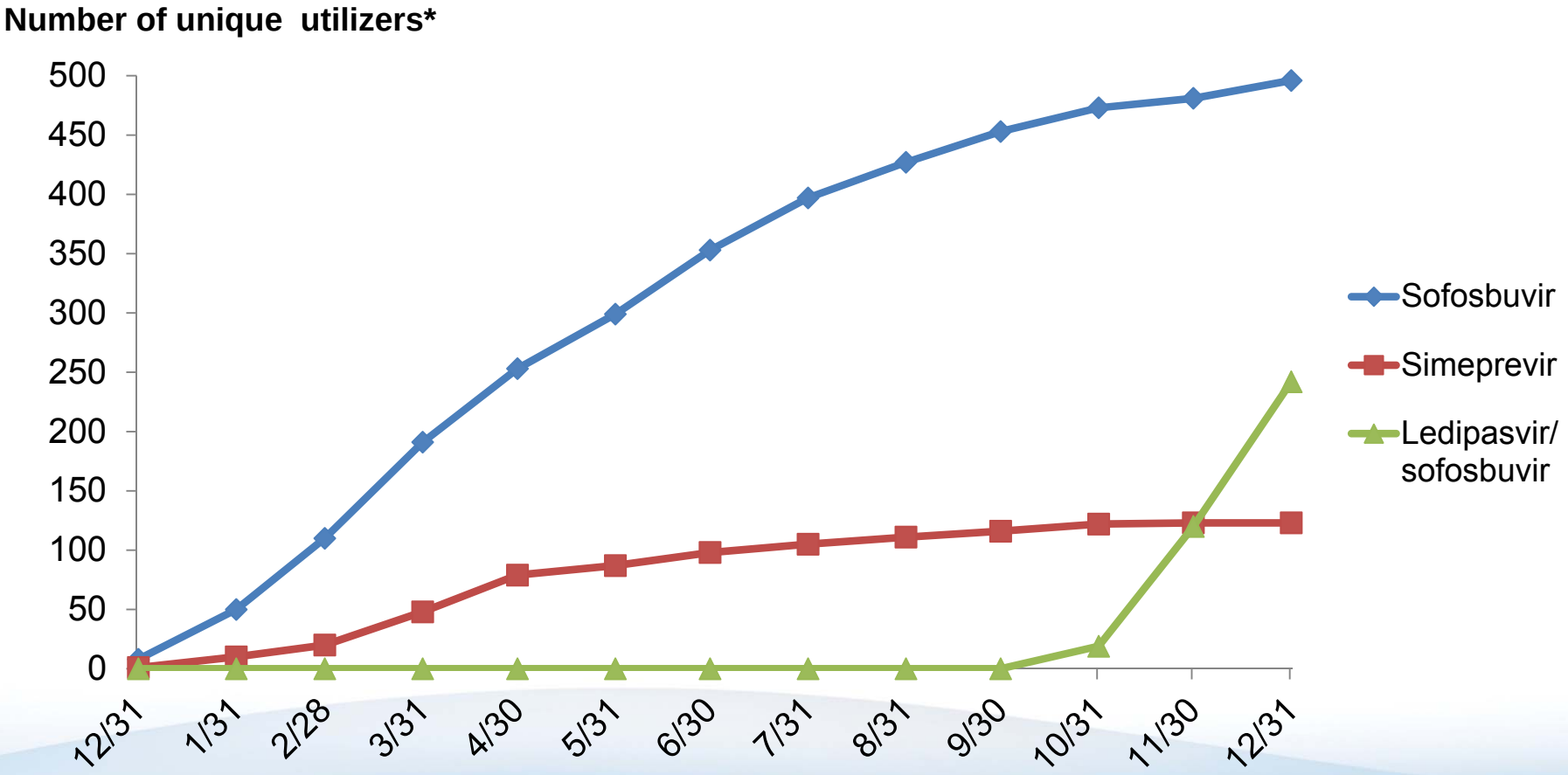
Novel Hepatitis C Agents

- New agents are changing hepatitis C treatment
  - Harvoni® (ledipasvir/sofosbuvir)
  - Viekira Pak™ (ombitasvir/paritaprevir/ritonavir; dasabuvir)
- Offer comparable efficacy in many patient populations
- Additional pill burden, side effects, drug interaction, contraindications, and differences in cost should be considered
- Several commercial payers have already negotiated favorable pricing with drug manufacturers

Current and Future Management Strategies

- Regimen selection and duration
  - HCV genotype and subtype
  - Compensated vs decompensated cirrhosis
  - Prior treatment history and response
  - Drug interactions and contraindications
- Promoting optimal adherence
  - Enrollment into case management
  - Refill reminder phone calls
- Futility rules
- Fibrosis: controversial
  - “Who to treat and when”
- Selection of a preferred regimen

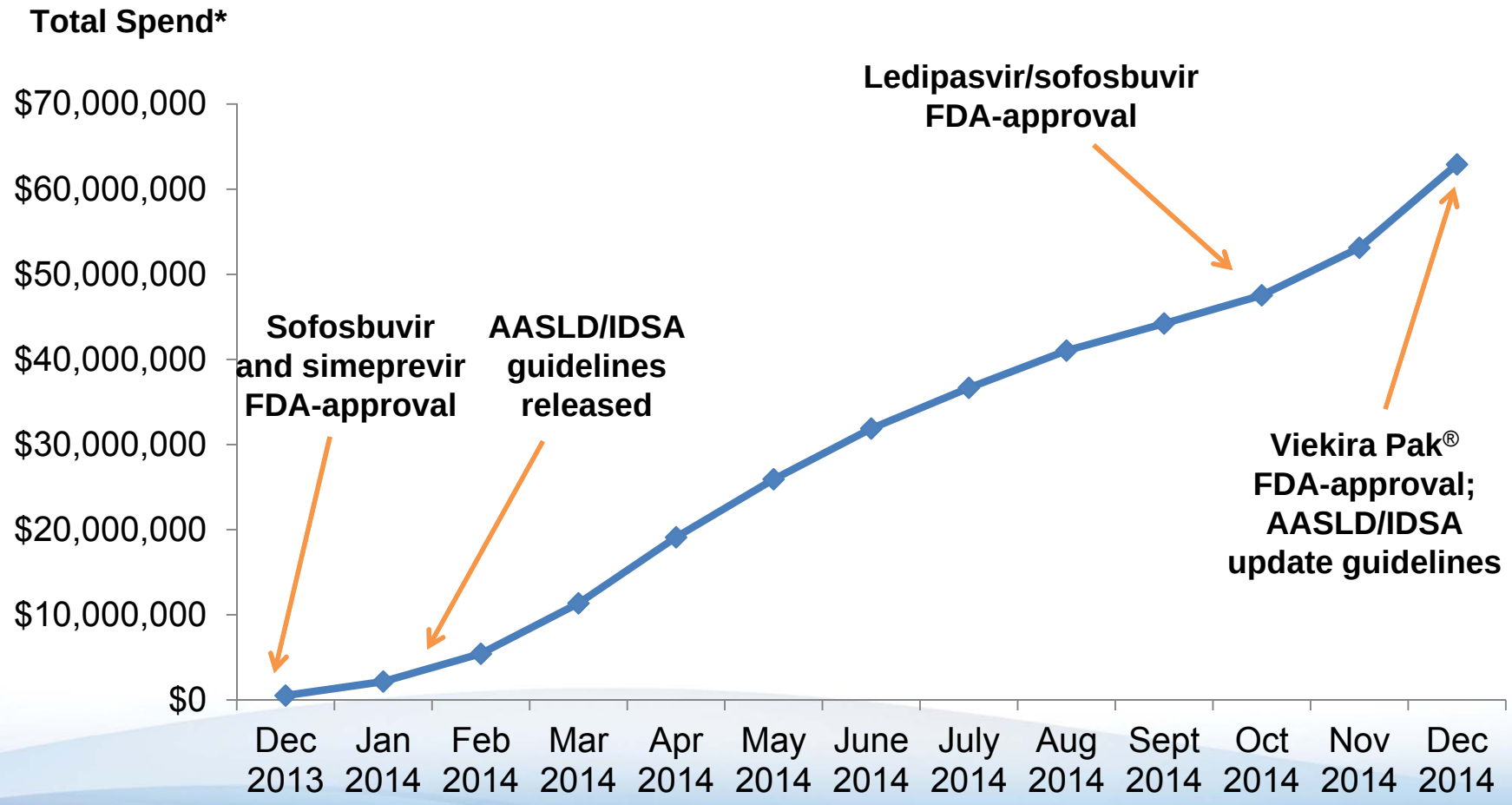
Trends in Utilization for 2014



*Excludes claims where state Medicaid is the secondary payor

University of Massachusetts Medical School
umassmed.edu

Total Pharmacy Spend on Hepatitis C Agents



*Total spend excludes claims where state Medicaid is the secondary payor
AASLD=American Association for the Study of Liver Diseases, FDA=Food and Drug Administration, IDSA=Infectious Diseases Society of America
Viekira Pak® (ombitasvir, paritaprevir and ritonavir; dasabuvir)

Treatment Completion and Cure Rates

December 18, 2013 – December 31, 2014

	Treatment completed based on pharmacy claims data	Due for 12-week post-therapy completion viral load	SVR*	Detectable viral load after treatment
Number of members	**380**	**286**	**138**	**31**

SVR=sustained virologic response; includes members with undetectable viral load at least 11 weeks after treatment completion

Conclusion

- New agents have dramatically improved cure rates in the treatment of hepatitis C
- High treatment costs necessitate careful screening for appropriate candidates, regimen selection, and adherence monitoring
- Hepatitis C monitoring program has shown promise in reducing costs and improving member care
- Lessons learned could be applicable to other medically complex disease states

Thank you!

Questions/Comments?

References

- AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed January 18, 2015.
- Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, Management and treatment of hepatitis C; An Update. 2009. Hepatology 2009; 49(4):1-40.
- Massachusetts Department of Public Health. Clinical Advisory: Routine Screening for Hepatitis C. http://www.mass.gov/eohhs/docs/dph/aids/hcv-clinical-advisory.pdf. Accessed January 30, 2015
- Sovaldi® (sofosbuvir) product eDossier. December 20, 2013. Version 3.1. Gilead Sciences. Accessed via secure log in to the AMCP eDossier System (https://amcp.edossiers.com) on December 20, 2013.
- Strader DB, Wright T, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. Hepatology. 2004 Apr;39(4):1147-71.
- US FDA. FDA Antiviral Drugs Advisory Committee Meeting October 25, 2013: Background Package for NDA 204671 Sofosbuvir (GS-7977). 2013 Oct [cited 2015 Jan 18]. Available from: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm371875.htm.