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Topics in Antiviral Medicine™

A publication of the IAS–USA

Perspective

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Special Contribution

Topics in Antiviral Medicine™

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Topics in Antiviral Medicine™

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Continuing Medical Education

Continuing medical education (CME) enduring material in this issue: Merlin JS, Tucker RO, Saag MS, Selwyn PA. The Role of Palliative Care in the Current HIV Treatment Era in Developed Countries. *Top Antiviral Med*. 2013;21(1):20-26

Overview

- CME credits available: 1.25 *AMA PRA Category 1 Credits*™
- Release date: March 29, 2013
- Expiration date: March 29, 2014

This enduring material provides a review of the role of palliative care in the current HIV treatment era. To complete the activity, read the article, successfully complete the posttest, submit the evaluation, and complete and submit the CME claim form. To claim CME credit, submit the claim form online or, for paper copies, via fax or mail.

The IAS–USA offers this state-of-the-art activity as part of a nationwide CME effort for physicians on the evolving challenges of managing HIV disease.

Learning Objectives

On completion of this activity, the learner will be able to:

- Describe the role of palliative care in contemporary HIV care
- Recognize opportunities for integration of palliative care with disease-specific care for patients with HIV throughout the course of disease
- List opportunities for dialogue between HIV and palliative care clinicians and researchers about ways to reduce HIV-infected patients' suffering and improve their physical function and quality of life

Intended Audience

This enduring material is designed for physicians who are actively involved in the medical care of people with HIV infection, specifically those who:

- Have a solid, working knowledge of HIV disease management
- Provide comprehensive or specialty care for patients with HIV infection
- Are currently active in HIV research

This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

CME Information

The International Antiviral Society–USA (IAS–USA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The IAS–USA designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is offered from March 29, 2013 to March 29, 2014. Participants who successfully complete the activity posttest and submit the evaluation and registration forms are eligible to receive CME Credit. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Other health care practitioners will receive a certificate of participation.

Disclosure of Financial Interests

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Financial Affiliations: Drs Merlin, Tucker, and Selwyn have no relevant financial affiliations to disclose (Updated 3/5/13). Dr Saag has received research support from and has been a scientific advisor to Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, Merck & Co, Inc, and ViiV Healthcare. He has served as a scientific advisor and consultant for Vertex Pharmaceuticals and has received additional research support from Boehringer Ingelheim Pharmaceuticals, Inc, and GlaxoSmithKline (Updated 3/5/13). Dr Richman has been a consultant to Biota, Bristol-Myers Squibb, Chimerix, Gen-Probe Inc, Gilead Sciences, Inc, Merck & Co, Inc, and Monogram Biosciences, Inc. He has held stock options for Chimerix (Updated 3/27/13). Dr Benson has no relevant financial affiliations to disclose (Updated 4/1/13). Dr Benson's spouse, Dr Robert T. Schooley, has served as a scientific advisory board member for Gilead Sciences, Inc, Monogram Biosciences, and GlobeImmune, Inc. He has served as scientific collaborator for MBio Diagnostics. He has received grant support from Boehringer Ingelheim and Bristol-Myers Squibb. He has stock in GlobeImmune, Inc. He has served as a consultant to Merck & Co, Inc, and Santaris Pharma A/S (Updated 3/27/13). Dr Hirsch has no relevant financial affiliations to disclose (Updated 3/27/13). Ms Jacobsen has no relevant financial affiliations to disclose (Updated 3/22/13).

Grant Support

This HIV activity is funded through independent, educational grants at a national level from commercial organizations that are committed to supporting high-quality continuing medical education (CME). We gratefully acknowledge the supporters of the 2013 *Improving the Management of HIV Disease* CME program.

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1. Palliative care is best described as:

- ❑ **A.** Care for patients in the end stages of a terminal illness
- ❑ **B.** Synonymous with hospice care
- ❑ **C.** Alleviating suffering while maximizing physical function
- ❑ **D.** Only available in inpatient settings

2. In the context of an aging HIV-infected patient with multiple medical comorbidities, a palliative care consultant should provide input and guidance on all of the following except:

- ❑ **A.** Physical and emotional symptoms
- ❑ **B.** Advanced care planning
- ❑ **C.** Interdisciplinary team support that includes nurses, social workers, and chaplains to assess and address the needs of the patient and family
- ❑ **D.** Antiretroviral therapy selection

3. In the context of an HIV-infected patient who has struggled with adherence to antiretroviral therapy and is dying with AIDS, a palliative care consultant should provide input and guidance on all of the following except:

- ❑ **A.** Antiretroviral therapy adherence
- ❑ **B.** The patient's goals of care, and complex medical decision making
- ❑ **C.** Physical, psychological, social, emotional, and spiritual aspects of suffering
- ❑ **D.** Psychiatric illness and addiction, in collaboration with specialists in these areas

4. End-stage cirrhosis in HIV-infected patients is best described as:

- ❑ **A.** An opportunity for palliative care consultation, to help with symptom burden and end-of-life care issues
- ❑ **B.** An uncommon cause of morbidity and mortality
- ❑ **C.** Not associated with symptoms such as pain or shortness of breath
- ❑ **D.** A contraindication to prescribing opioids and benzodiazepines

5. End-of-life care issues in HIV-infected patients that merit attention include all of the following except:

- ❑ **A.** Advanced care planning, including identifying a health care proxy
- ❑ **B.** Mood disorders and addiction
- ❑ **C.** Risks and benefits of procedures such as the insertion of a feeding tube
- ❑ **D.** If and when to stop antiretroviral therapy
- ❑ **E.** Counseling patients to continue taking antiretroviral therapy

To claim CME credit, please successfully complete the posttest and evaluation form, which will help us evaluate this activity and plan future activities. Your responses will not affect your CME credit. Fill out the test and the evaluation online at www.iasusa.org or mail or fax this page along with the completed test to: IAS–USA, 425 California Street, Suite 1450, San Francisco, CA 94104-2120; Fax: (415) 544-9401

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Evaluation

Please rate this activity in terms of meeting each of its stated objectives.

	Excellent	Very Good	Good	Fair	Poor
Describe the role of palliative care in contemporary HIV care	❍	❍	❍	❍	❍
Recognize opportunities for integration of palliative care with disease-specific care for patients with HIV throughout the course of disease	❍	❍	❍	❍	❍
List opportunities for dialogue between HIV and palliative care clinicians and researchers about ways to reduce HIV-infected patients' suffering and improve their physical function and quality of life	❍	❍	❍	❍	❍

How challenging was this activity? ❒ Highly challenging ❒ Sufficiently challenging ❒ Insufficiently challenging

Please rate this activity based on:

	Excellent	Very Good	Good	Fair	Poor
Quality of this activity overall	❍	❍	❍	❍	❍
Overall value of this activity to your practice or responsibility	❍	❍	❍	❍	❍
The extent to which the information presented was supported by the evidence	❍	❍	❍	❍	❍
Freedom from commercial bias	❍	❍	❍	❍	❍

Do you expect to make changes in your clinical practice based on the information presented in this activity? ❒ Yes ❒ No

If so, please list 3 measurable changes you expect to make:

1. _____
2. _____
3. _____

Other comments (please feel free to comment on any aspect of this enduring material or *Topics in Antiviral Medicine*™):

_____

_____

How many HIV-infected patients do you personally manage?
❒ None ❒ 1–4 ❒ 5–10 ❒ 11–15 ❒ 16–50 ❒ 51–100 ❒ 101–200 ❒ More than 200

How many HIV-infected patients are in your clinic overall?
❒ None ❒ 1–4 ❒ 5–10 ❒ 11–15 ❒ 16–50 ❒ 51–100 ❒ 101–200 ❒ More than 200

Please rate your expertise in treating HIV infection: ❒ 1 (novice) ❒ 2 ❒ 3 ❒ 4 ❒ 5 (expert)

2013 Live Continuing Medical Education Courses

IAS–USA CME course announcements are paperless. Please watch for e-mail updates, and visit www.iasusa.org for general course information, agendas, and online registration. Early registration is strongly recommended. These live activities have been approved for *AMA PRA Category 1 Credit.*™

Evolving Strategies in Hepatitis C Virus Management

Part of the IAS–USA focus on the management of HCV infection, these half-day, small-group, intensive CME workshops are presented by leading experts in the field. Attendance is limited to 35 practitioners, so early registration is encouraged.

Atlanta, Georgia
Tuesday, April 9, 2013
Cobb Galleria Centre

Los Angeles, California
Tuesday, April 23, 2013
Center for Healthy Communities
(California Endowment Center)

Chicago, Illinois
Tuesday, May 21, 2013
Chicago Marriott Downtown Magnificent Mile

Washington, DC, area
Monday, June 17, 2013
Hyatt Regency Crystal City

Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes

The full-day advanced CME course is designed for clinicians who are experts in the complexities of antiretroviral management and who are well-positioned to join their hepatology and gastroenterology colleagues in providing care for hepatitis C virus–infected patients, in what has become an exciting new era in hepatitis C virus care.

South San Francisco, California
Tuesday, June 4, 2013
South San Francisco Conference Center
Cochairs: Marion G. Peters, MD, David L. Wyles, MD

New York, New York
Tuesday, June 25, 2013
New York Marriott Marquis
Cochairs: Robert T. Schooley, MD
David L. Thomas, MD, MPH

Improving the Management of HIV Disease®

The annual full-day advanced CME courses continue to focus on cutting-edge, scientifically rigorous issues presented by leading experts in the field, providing the latest insights and data on the full spectrum of HIV- and AIDS-related treatment issues.

San Francisco, California
Friday, March 29, 2013
Mission Bay Conference Center
Cochairs: Stephen E. Follansbee, MD
Robert T. Schooley, MD

Atlanta, Georgia
Wednesday, April 10, 2013
Cobb Galleria Centre
Cochairs: Jeffrey L. Lennox, MD, Michael S. Saag, MD

Los Angeles, California
Monday, April 22, 2013
Center for Healthy Communities
(California Endowment Center)
Cochairs: Constance A. Benson, MD, FACP
Ronald T. Mitsuyasu, MD

New York, New York
Friday, May 3, 2013
New York Marriott Marquis
Cochairs: Gerald H. Friedland, MD
Paul A. Volberding, MD

Chicago, Illinois
Monday, May 20, 2013
Chicago Marriott Downtown Magnificent Mile
Cochairs: John P. Phair, MD, Paul A. Volberding, MD

Washington, DC, area
Tuesday, June 18, 2013
Hyatt Regency Crystal City
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Special Contribution

Update of the Drug Resistance Mutations in HIV-1: March 2013

Victoria A. Johnson, MD, Vincent Calvez, MD, PhD, Huldrych F. Günthard, MD, Roger Paredes, MD, PhD, Deenan Pillay, MD, PhD, Robert W. Shafer, MD, Annemarie M. Wensing, MD, PhD, and Douglas D. Richman, MD

This March 2013 edition of the IAS–USA drug resistance mutations list updates the figures last published in November 2011.[1]

In this update, 2 integrase strand transfer inhibitors (InSTIs), elvitegravir and dolutegravir, have become available and were added to the figure. Elvitegravir was approved by the US Food and Drug Administration (FDA) in August 2012 for HIV-1 treatment-naive patients as part of a fixed-dose combination of elvitegravir/cobicistat/tenofovir/emtricitabine.[2,3] Dolutegravir is being evaluated in clinical trials for both initial HIV therapy and for use by treatment-experienced patients. It is available in an expanded access program and has been designated for priority review by the US FDA for treatment-experienced patients with detectable viral load who have documented HIV-1 resistance to raltegravir or elvitegravir. Relevant elvitegravir and dolutegravir mutations that have been identified to date are listed on the figure.

The following mutations have been added to existing classes or drugs: M230L has been added to the bars for the nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine;[4,5] Y188L has been added to the NNRTI rilpivirine bar; the asterisk was removed from E138K (see revised user note).[6,7] L74M, T97A, E138A/K, and G140A/S have been added to the InSTI raltegravir bar; E92Q was unbolded.

Methods

The IAS–USA Drug Resistance Mutations Group is an independent, volunteer panel of experts charged with delivering accurate, unbiased, and evidence-based information on these mutations to HIV clinical practitioners. As with all IAS–USA volunteer panels, members are rotated on a structured, planned basis. The group reviews new data on HIV drug resistance to maintain a current list of mutations associated with clinical resistance to HIV. This list includes mutations that may contribute to a reduced virologic response to a drug.

In addition, the group considers only data that have been published or have been presented at a scientific conference. Drugs that have been approved by the US FDA as well as any drugs available in expanded access programs are included (listed in alphabetical order by drug class). User notes provide additional information as necessary. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive.

Identification of Mutations

The mutations listed are those that have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) nucleotide sequencing of viruses from patients in whom the drug is failing; (4) association studies between genotype at baseline and virologic response in patients exposed to the drug.

The development of more recently approved drugs that cannot be tested as monotherapy precludes assessment of the impact of resistance on antiretroviral activity that is not seriously confounded by activity of other drug components in the background regimen. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact. Polymorphisms associated with impaired treatment responses that occur in otherwise wild-type viruses should not be used in epidemiologic analyses to identify transmitted HIV-1 drug resistance.

Clinical Context

The figures are designed for practitioners to use in identifying key mutations associated with antiretroviral drug resistance and in making therapeutic decisions. In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV-1 genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient's antiretroviral therapy history; (2) recognizing that in the absence of drug (selection pressure), resistant strains may be present at levels below the limit of detection of the test (analyzing stored samples, collected under selection pressure, could be useful in this setting); and (3) recognizing that virologic failure of the first regimen typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in the regimen (in this setting, resistance develops most commonly to lamivu-

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dine or emtricitabine or the nonnucleoside analogue reverse transcriptase inhibitors [NNRTIs]).

The absence of detectable viral resistance after treatment failure may result from any combination of the following factors: the presence of drug-resistant minority viral populations, a prolonged interval between the time of antiretroviral drug discontinuation and genotypic testing, nonadherence to medications, laboratory error, lack of current knowledge of the association of certain mutations with drug resistance, the occurrence of relevant mutations outside the regions targeted by routine resistance assays, drug-drug interactions leading to subtherapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.

For more in-depth reading and an extensive reference list, see the 2008 IAS–USA panel recommendations for resistance testing[8] and 2012 IAS–USA panel recommendations for antiretroviral therapy.[9] Updates are posted periodically at www.iasusa.org.

Comments

Please send your evidence-based comments, including relevant reference citations, to the **journal"at"iasusa.org** or by fax at 415-544-9401.

Reprint Requests

The Drug Resistance Mutations Group welcomes interest in the mutations figures as an educational resource for practitioners and encourages dissemination of the material to as broad an audience as possible. However, permission is required to reprint the figures and **no alterations in format or the content can be made**.

Requests to reprint the material should include the name of the publisher or sponsor, the name or a description of the publication in which you wish to reprint the material, the funding organization(s), if applicable, and the intended audience. Requests to make any minimal adaptations of the material should include the former, plus a detailed explanation of the adaptation(s) and, if possible, a copy of the proposed adaptation. To ensure the integrity of the mutations figures, IAS–USA policy is to grant permission for only minor, preapproved adaptations of the figures (eg, an adjustment in size). Minimal adaptations only will be considered; no alterations of the content of the figures or user notes will be permitted.

Permission will be granted only for requests to reprint or adapt the most current version of the mutations figures as they are posted on www.iasusa.org. Because scientific understanding of HIV drug resistance evolves rapidly and the goal of the Drug Resistance Mutations Group is to maintain the most up-to-date compilation of mutations for HIV clinicians and researchers, publication of out-of-date figures is counterproductive. If you have any questions about reprints or adaptations, please contact the IAS–USA.

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Top Antivir Med. 2013;21(1):6-14

MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)[a]

Multi-nRTI Resistance: 69 Insertion Complex[b] (affects all nRTIs currently approved by the US FDA)

M	A	▼	K	L	T	K
41	**62**	**69**	**70**	**210**	**215**	**219**
L	**V**	**Insert**	**R**	**W**	**Y**	**Q**
					F	**E**

Multi-nRTI Resistance: 151 Complex[c] (affects all nRTIs currently approved by the US FDA except tenofovir)

A	V	F	F	Q
62	**75**	**77**	**116**	**151**
V	**I**	**L**	**Y**	**M**

Multi-nRTI Resistance: Thymidine Analogue-Associated Mutations[d,e] (TAMs; affect all nRTIs currently approved by the US FDA)

M	D	K	L	T	K
41	**67**	**70**	**210**	**215**	**219**
L	**N**	**R**	**W**	**Y**	**Q**
				F	**E**

	K	L	Y	M
Abacavir[f,g]	**65**	**74**	**115**	**184**
	R	**V**	**F**	**V**
Didanosine[g,h]	**65**	**74**		
	R	**V**		
Emtricitabine	**65**			**184**
	R			**V**
				I
Lamivudine	**65**			**184**
	R			**V**
				I

	M	K	D	K	L	T	K
Stavudine[d,e,g,i,j,k]	**41**	**65**	**67**	**70**	**210**	**215**	**219**
	L	**R**	**N**	**R**	**W**	**Y**	**Q**
						F	**E**
Tenofovir[l]		**65**		**70**			
		R		**E**			
Zidovudine[d,e,j,k]	**41**		**67**	**70**	**210**	**215**	**219**
	L		**N**	**R**	**W**	**Y**	**Q**
						F	**E**

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)[a,m]

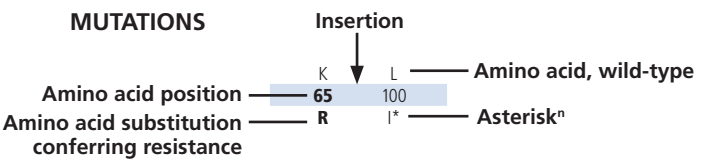
	L	K	K	V	V	Y	Y	G	P	M
Efavirenz	**100**	**101**	**103**	**106**	**108**	**181**	**188**	**190**	**225**	**230**
	I	**P**	**N**	**M**	**I**	**C**	**L**	**S**	**H**	**L**
			S			**I**		**A**		

	V	A	L	K		V	E	V	Y		G		M
Etravirine[n]	90	98	**100**	**101**		106	138	179	**181**		190		230
	I	G	**I***	E		I	A	D	**C***		S		L
				H			G	F	**I***		A		
				P*			K	T	**V***				
							Q						

	L	K	K	V	V	Y	Y	G	M
Nevirapine	**100**	**101**	**103**	**106**	**108**	**181**	**188**	**190**	**230**
	I	**P**	**N**	**A**	**I**	**C**	**C**	**A**	**L**
			S	**M**		**I**	**L**		
							H		

	K	E	V	Y	Y	H	F	M
Rilpivirine[o]	**101**	**138**	**179**	**181**	**188**	**221**	**227**	**230**
	E	**A**	**L**	**C**	**L**	**Y**	**C**	**I**
	P	**G**		**I**				**L**
		K		**V**				
		Q						
		R						

Amino acid abbreviations: A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.



MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS[p,q,r]

	L	G	K	L	V	L	E	M	M	G	I	F	I	D	I	I	A	G	V	I	I	N	L	I
Atazanavir +/- ritonavir[s]	10	16	20	24	32	33	34	36	46	48	**50**	53	54	60	62	64	71	73	82	**84**	85	**88**	90	93
	I	E	R	I	I	I	Q	I	I	V	L	L	L	E	V	L	V	C	A	V	V	V	S	M	L
	F		M			F		L	L			Y	M			M	I	S	F	T					M
	V		I			V		V					T				T	T	I						
	C		T										A				L	A							
	V				V	L			I		I		I						T	L			L		
Darunavir/ ritonavir[t]	11				32	33			**47**		**50**		**54**						74	**76**		**84**	89		
	I				I	F			V		V		M						P	V		V	V		
													L												
	L				V				M	I	I		I					G	L		V	I		L	
Fosamprenavir/ ritonavir	10				32				46	47	**50**		54					73	76		82	**84**		90	
	F				I				I	V	V		L					S	V		A	V		M	
	I								L				V								F				
	R												M								S				
	V																				T				
	L		K	L	V			M	M				I				A	G	L	V	V	I		L	
Indinavir/ ritonavir[u]	10		20	24	32			36	**46**				54				71	73	76	77	**82**	**84**		90	
	I		M	I	I			I	I				V				V	S	V	I	A	V		M	
	R		R						L								T	A	I		F				
	V																				T				
	L		K	L	V	L			M	I	I	F	I		L		A	G	L		V	I		L	
Lopinavir/ ritonavir[v]	10		20	24	**32**	33			46	**47**	50	53	54		63		71	73	**76**		**82**	84		90	
	F		M	I	I	F			I	V	V	L	V		P		V	S	V		A	V		M	
	I		R						L	A			L				T				F				
	R												A								T				
	V												M								S				
													T												
	L				D			M	M								A		V	V	V	I	N	L	
Nelfinavir[u,w]	10				**30**			36	46								71		77	V	82	84	88	**90**	
	F				N			I	I								V		I		A	V	D	M	
	I								L								T				F		S		
																					T				
	L			L						G		I		I			A	G		V	V	I		L	
Saquinavir/ ritonavir[u]	10			24						**48**		54		62			71	73		77	82	84		**90**	
	I			I						V		V		V			V	S		I	A	V		M	
	R											L					T				F				
	V																				S				
	L					L		M			K	M	I		Q			H		T		V	N	I		L	
Tipranavir/ ritonavir[x]	10					33		36			43	46	**47**		54	**58**		69		**74**		**82**	**83**	**84**		89	
	V					F		I			T	L	V		A	E		K		P		L	D	V		I	
								L							M			R				T				M	
								V							V												V	

MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

	G	I	V	Q	Q	N	N
Enfuvirtide[y]	**36**	**37**	**38**	**39**	**40**	**42**	**43**
	D	**V**	**A**	**R**	**H**	**T**	**D**
	S		**M**				
			E				

Maraviroc[z]	See User Note

MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS

	E	G	Q
Dolutegravir[aa]	**138**	**140**	**148**
	A	**S**	**H**
	K	A	

	T	E	T	S	Q	N
Elvitegravir[bb]	**66**	**92**	**97**	**147**	**148**	**155**
	I	**Q**	A	**G**	**R**	**H**
	A	C			H	
	K				K	

	L	E	T	E	G	Y	Q	N
Raltegravir[cc]	**74**	**92**	**97**	**138**	**140**	**143**	**148**	**155**
	M	Q	A	A	A	**R**	**H**	**H**
				K	S	**H**	**K**	
						C	**R**	

User Notes

a. Some nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) mutations, like T215Y and H208Y,[1] may lead to viral hypersusceptibility to the non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), including etravirine,[2] in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens (nevirapine or efavirenz) in NNRTI-naive individuals,[3-7] although no clinical data exist for improved response to etravirine in NNRTI-experienced individuals. Mutations at the C-terminal reverse transcriptase domains (amino acids 293-560) outside of regions depicted on the figure bars may prove to be important for nRTI and NNRTI HIV-1 drug resistance. The clinical relevance of these connection domain mutations arises mostly in conjunction with thymidine analogue-associated mutations (TAMs) and M184V and have not been associated with increased rates of virologic failure of etravirine or rilpivirine in clinical trials.[8-10]

b. The 69 insertion complex consists of a substitution at codon 69 (typically T69S) and an insertion of 2 or more amino acids (S-S, S-A, S-G, or others). The 69 insertion complex is associated with resistance to all nRTIs currently approved by the US FDA when present with 1 or more TAMs at codons 41, 210, or 215.[11] Some other amino acid changes from the wild-type T at codon 69 without the insertion may be associated with broad nRTI resistance.

c. Tenofovir retains activity against the Q151M complex of mutations.[11] Q151M is the most important mutation in the complex (ie, the other mutations in the complex [A62V, V75I, F77L, and F116Y] in isolation may not reflect multidrug resistance).

d. Mutations known to be selected by TAMs (ie, M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) also confer reduced susceptibility to all currently approved nRTIs.[12] The degree to which cross-resistance is observed depends on the specific mutations and number of mutations involved.[13-16]

e. Although reverse transcriptase changes associated with the E44D and V118I mutations may have an accessory role in increased resistance to nRTIs in the presence of TAMs, their clinical relevance is very limited.[17-19]

f. The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo. When associated with TAMs, M184V increases abacavir resistance.[20,21]

g. As with tenofovir, the K65R mutation may be selected by didanosine, abacavir, or stavudine (particularly in patients with nonsubtype-B clades) and is associated with decreased viral susceptibility to these drugs.[20,22,23] Data are lacking on the potential negative impact of K65R on clinical response to didanosine.

h. The presence of 3 of the following mutations—M41L, D67N, L210W, T215Y/F, K219Q/E—is associated with resistance to didanosine.[24] The presence of K70R or M184V alone does not decrease virologic response to didanosine.[25]

i. K65R is selected frequently (4% – 11%) in patients with nonsubtype-B clades for whom stavudine-containing regimens are failing in the absence of tenofovir.[26,27]

j. The presence of M184V appears to delay or prevent emergence of TAMs.[28] This effect may be overcome by an accumulation of TAMs or other mutations.

k. The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations at codon 215 that confer increased risk of virologic failure of zidovudine or stavudine in antiretroviral-naive patients.[29,30] The T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine.[31]

l. The presence of K65R is associated with a reduced virologic response to tenofovir.[11] A reduced response also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W.[11] The presence of TAMs or combined treatment with zidovudine prevents the emergence of K65R in the presence of tenofovir.[32-34]

m. The sequential use of nevirapine and efavirenz (in either order) is not recommended because of cross-resistance between these drugs.[35]

n. Resistance to etravirine has been extensively studied only in the context of coadministration with darunavir/ritonavir. In this context, mutations associated with virologic outcome have been assessed and their relative weights (or magnitudes of impact) assigned. In addition, phenotypic cutoff values have been calculated, and assessment of genotype-phenotype correlations from a large clinical database have determined relative importance of the various mutations. These 2 approaches are in agreement for many, but not all, mutations and weights.[36-38] Asterisks (*) are used to emphasize higher relative weights with regard to reduced susceptibility and reduced clinical response compared with other etravirine mutations.[39] The single mutations L100I*, K101P*, and Y181C*/I*/V* reduce clinical utility. The presence of K103N alone does not affect etravirine response.[40] Accumulation of several mutations results in greater reductions in susceptibility and virologic response than do single mutations.[41-43]

o. Fifteen mutations have been associated with decreased rilpivirine susceptibility (K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H221Y, F227C, and M230I/L).[44-46] A 16th mutation, Y188L, reduces rilpivirine susceptibility 6 fold.[47] K101P and Y181I/V reduce rilpivirine susceptibility approximately 50 fold and 15 fold, respectively, but are uncommonly observed in patients receiving rilpivirine.[48-50] K101E, E138K, and Y181C, each of which reduces rilpivirine susceptibility 2.5 fold to 3 fold, occur commonly in patients receiving rilpivirine. E138K and to a lesser extent K101E usually occur in combination with the nRTI resistance mutation M184I, which alone does not reduce rilpivirine susceptibility. When M184I is combined with E138K or K101E, rilpivirine susceptibility is reduced approximately 7 fold and 4.5 fold, respectively.[50-53]

p. Often, numerous mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI).[54] In some specific circumstances, atazanavir might be used unboosted. In such cases, the mutations that are selected are the same as with ritonavir-boosted atazanavir, but the relative frequency of mutations may differ.

q. Resistance mutations in the protease gene are classified as "major" or "minor."

Major mutations in the protease gene (positions in **bold** type) are defined as those selected first in the presence of the drug or those substantially reducing drug susceptibility. These mutations tend to be the primary contact residues for drug binding.

Minor mutations generally emerge later than major mutations and by themselves do not have a substantial effect on phenotype. They may improve replication of viruses containing major mutations. Some minor mutations are present as common polymorphic changes in HIV-1 nonsubtype-B clades.

r. Ritonavir is not listed separately, as it is currently used only at low dose as a pharmacologic booster of other PIs.

s. Many mutations are associated with atazanavir resistance. Their impacts differ, with I50L, I84V, and N88S having the greatest effect. Higher atazanavir levels obtained with ritonavir boosting increase the number of mutations required for loss of activity. The presence of M46I plus L76V might increase susceptibility to atazanavir when no other related mutations are present.[55]

t. HIV-1 RNA response to ritonavir-boosted darunavir correlates with baseline susceptibility and the presence of several specific PI mutations. Reductions in response are associated with increasing numbers of the mutations indicated in the figure bar. The negative impact of the protease mutations I47V, I54M, T74P, and I84V and the positive impact of

the protease mutation V82A on virologic response to darunavir/ritonavir were shown in 2 data sets independently.[56,57] Some of these mutations appear to have a greater effect on susceptibility than others (eg, I50V vs V11I). A median darunavir phenotypic fold-change greater than 10 (low clinical cutoff) occurs with 3 or more of the 2007 IAS–USA mutations listed for darunavir[58] and is associated with a diminished virologic response.[59]

u. The mutations depicted on the figure bar cannot be considered comprehensive because little relevant research has been reported in recent years to update the resistance and cross-resistance patterns for this drug.

v. In PI-experienced patients, the accumulation of 6 or more of the mutations indicated on the figure bar is associated with a reduced virologic response to lopinavir/ritonavir.[60,61] The product information states that accumulation of 7 or 8 mutations confers resistance to the drug.[62] However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I, are associated with high-level resistance.[63-65] The addition of L76V to 3 PI resistance-associated mutations substantially increases resistance to lopinavir/ritonavir.[55]

w. In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI mutations.[66]

x. Clinical correlates of resistance to tipranavir are limited by the paucity of clinical trials and observational studies of the drug. The available genotypic scores have not been validated on large, diverse patient populations. The presence of mutations L24I, I50L/V, F53Y/L/W, I54L, and L76V have been associated with improved virologic response to tipranavir in some studies.[67-69]

y. Resistance to enfuvirtide is associated primarily with mutations in the first heptad repeat (HR1) region of the gp41 envelope gene. However, mutations or polymorphisms in other regions of the envelope (eg, the HR2 region or those yet to be identified) as well as coreceptor usage and density may affect susceptibility to enfuvirtide.[70-72]

z. The activity of CC chemokine receptor 5 (CCR5) antagonists is limited to patients with virus that uses only CCR5 for entry (R5 virus). Viruses that use both CCR5 and CXC chemokine receptor 4 (CXCR4; termed dual/mixed [D/M] virus) or only CXCR4 (X4 virus) do not respond to treatment with CCR5 antagonists. Virologic failure of these drugs frequently is associated with outgrowth of D/M or X4 virus from a preexisting minority population present at levels below the limit of assay detection. Mutations in HIV-1 gp120 that allow the virus to bind to the drug-bound form of CCR5 have been described in viruses from some patients whose virus remained R5 after virologic failure of a CCR5 antagonist. Most of these mutations are found in the V3 loop, the major determinant of viral tropism. There is as yet no consensus on specific signature mutations for CCR5 antagonist resistance, so they are not depicted in the figure. Some CCR5 antagonist-resistant viruses selected in vitro have shown mutations in gp41 without mutations in V3;[73] the clinical significance of such mutations is not yet known.

aa. Cross-resistance studies with raltegravir- and elvitegravir-resistant viruses in vitro indicate that Q148H and G140S in combination with mutations L74I/M, E92Q, T97A, E138A/K, G140A, or N155H are associated with 5-fold to 20-fold reduced dolutegravir susceptibility[74] and reduced virologic suppression in patients.[75-81] Results of the phase III dolutegravir study in antiretroviral treatment-naive patients are expected to provide additional resistance information.

bb. Six elvitegravir codon mutations have been observed in integrase strand transfer inhibitor treatment-naive and -experienced patients in whom therapy is failing.[82-88] T97A results in only a 2-fold change in elvitegravir susceptibility and may require additional mutations for resistance.[85,86] The sequential use of elvitegravir and raltegravir (in either order) is not recommended because of cross-resistance between these drugs.[85]

cc. Raltegravir failure is associated with integrase mutations in at least 3 distinct, but not exclusive, genetic pathways defined by 2 or more mutations including (1) a signature (major) mutation at Q148H/K/R, N155H, or Y143R/H/C; and (2) 1 or more additional minor mutations. Minor mutations described in the Q148H/K/R pathway include L74M plus E138A, E138K, or G140S. The most common mutational pattern in this pathway is Q148H plus G140S, which also confers the greatest loss of drug susceptibility. Mutations described in the N155H pathway include this major mutation plus either L74M, E92Q, T97A, E92Q plus T97A, Y143H, G163K/R, V151I, or D232N.[89] The Y143R/H/C mutation is uncommon.[90-94] E92Q alone reduces susceptibility to elvitegravir more than 20 fold and causes limited (< 5 fold) cross resistance to raltegravir.[84,95-97] N155H mutants tend to predominate early in the course of raltegravir failure but are gradually replaced by viruses with higher resistance, often bearing mutations G140S plus Q148H/R/K, with continuing raltegravir treatment.[90]

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Perspective

The Hidden Epidemic of Hepatitis C Virus Infection in the United States: Occult Transmission and Burden of Disease

Society faces an immense burden of hepatitis C virus (HCV) infection-related morbidity and mortality. Transmission of HCV is ongoing, and the incidence of HCV infection has been increasing in recent years. New therapies for treating HCV infection hold considerable promise for increasing cure rates and thus reducing HCV transmission. However, many persons with HCV infection in the United States are unaware of their infection status. The Centers for Disease Control and Prevention (CDC) recently expanded its HCV testing recommendations to include 1-time HCV testing for individuals born between 1945 and 1965, a population with a 3% prevalence of infection. Linkage to care and treatment for those identified with infection through testing would have a profound impact in reducing HCV disease burden. Coordinated efforts by public health agencies, clinical care providers, laboratories, and payers are necessary to improve primary and secondary prevention of HCV disease. This article summarizes a presentation by John W. Ward, MD, at the IAS–USA live continuing medical education program held in Atlanta, Georgia, in October 2012.

The United States is reaching a crucial point in the epidemic of hepatitis C virus (HCV)-related disease. One major issue we face is the inadequate number of practitioners who are trained, equipped, and willing to take care of the large population of people who are becoming progressively ill with this chronic infection.

HCV Morbidity and Mortality: The Grim Statistics

Acute HCV infection is characterized by mild to moderate symptoms in approximately 30% to 40% of patients. Although mortality from acute HCV is rare, approximately 75% of patients with accute infection become chronically infected. Chronic HCV infection is the cause of almost all HCV-related morbidity and mortality. After 30 years of chronic HCV infection, cirrhosis occurs in 15% to 35% of patients, and of these patients, there is a 1% to 3% incidence of hepatocellular carcinoma (HCC) each year. HCV infection increases the risk for HCC 17-fold, and 31% to 61% of HCC cases have markers of HCV infection. Approximately 36% of persons on the liver transplant waiting list have HCV-related liver disease. The lifetime risk of HCV-related death in chronic HCV infection is estimated at 37%.

Worldwide, approximately 170 million people have chronic HCV infection. Approximately 25% of persons infected with HIV also have HCV infection, with coinfection rates reported to be greater than 75% in some regions, such as China, Vietnam, and Russia. It is estimated that 2.7 million to 3.9 million people in the United States have chronic HCV infection and that more than 15,000 die each year from HCV-related disease, with mortality expected to rise in the coming years. Prevalence estimates for the United States are low, because they include only the noninstitutionalized civilian population and do not account for incarcerated or homeless persons, both being populations with high prevalences of HCV infection. Age-adjusted HCV-related mortality has been steadily increasing, with a 50% increase in rate occurring between 1999 and 2007. In 2007, HCV-related mortality exceeded HIV-related mortality, and data for 2008 indicate that the difference between the 2 rates continues to increase. More than 70% of registered deaths of HCV-infected individuals in 2007 were in those born from 1945 to 1965.

Figure 1 shows the staggering predicted future burden of HCV-related morbidity and mortality in the United States.[1] On the assumption that there are 2.7 million HCV-infected people in primary care, an estimated 1.47 million will develop cirrhosis, 350,000 will develop liver cancer, and 897,000 will die from HCV-related complications. Peaks in the prevalence of decompensated cirrhosis, HCC, and death are expected in the late 2020s and early 2030s.

HCV Transmission Continues

The HCV-related mortality trend reflects, in large part, the epidemic of HCV transmission in the years before the virus was discovered in 1989. It is

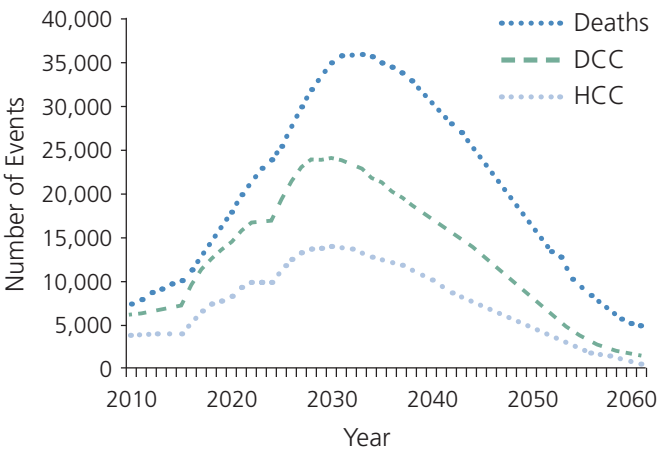

Figure 1. Future burden of hepatitis C virus (HCV)-related morbidity and mortality in the United States. DCC indicates decompensated cirrhosis; HCC, hepatocellular carcinoma. Adapted from Rein DB et al.[1]

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estimated that some 300,000 people in the United States became infected each year during that period, primarily through injection drug use (or user, IDU) practices and transfusions before the advent of blood screening and prevention strategies. The incidence of infection has since declined to approximately 15,000 to 20,000 cases per year.

Since reaching a nadir in 2005, the incidence of HCV infection in the United States has gradually increased, with a relatively dramatic increase in 2011. Figure 2 shows the age distribution of confirmed HCV cases in Massachusetts in 2002 and 2009.[2] There has been a marked increase in number of infections reported in people in their 20s and early 30s since 2002, and similar findings have been reported from other states including Pennsylvania and Wisconsin. Most of these cases in younger persons involve current or past IDU. These individuals are predominantly white, equally proportioned by sex, very commonly previous users of narcotics such as oxycodone, and predominantly from suburban and rural settings—a characteristic that makes case investigation more difficult.

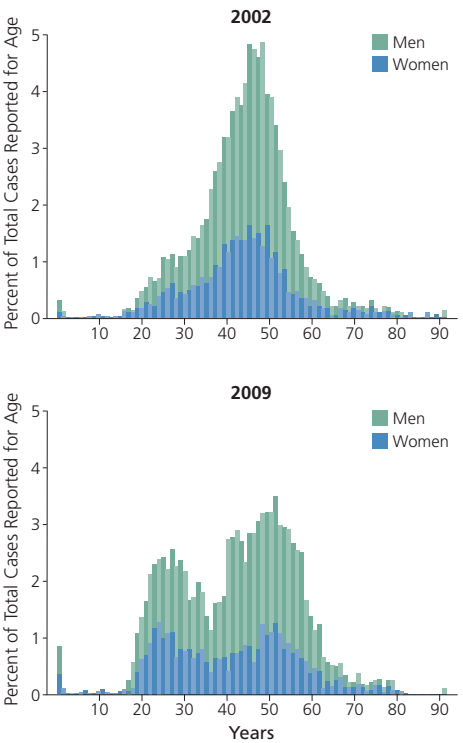

Figure 2. Age distribution of confirmed hepatitis C virus (HCV) cases in Massachusetts in 2002 (top) and 2009 (bottom). Adapted from Centers for Disease Control and Prevention.[2]

IDU. IDUs remain at highest risk for HCV infection. Globally, it is estimated that 64% of IDUs have HCV infection. IDU accounts for 60% to 70% of new infections in the United States and many other countries. Acquisition of HCV is fairly rapid after the start of IDU, with incidence being highest among new injectors; the estimated rate of infection within 2 years of beginning IDU is 18 to 27 per 100 person-years. Reinfection after HCV clearance is not uncommon, estimated at 1.8 to 4.7 cases per 100 person-years. The lower rate of reinfection than initial infection appears to reflect a protective effect of immune priming during initial infection.

The availability of oral direct-acting antivirals (DAAs) for HCV therapy has raised the prospect of reducing the "force" of infection by lowering the prevalence of infection in networks of those who inject drugs. Figure 3 shows projections of relative prevalence reductions based on different assumptions for numbers of infected people treated per 1000 IDU population and an assumed sustained virologic response (SVR) rate of 62.5%.[3] For example, it is estimated that treating 10 HCV infections per year per 1000 IDUs with an SVR rate of 62.5% would result in a relative reduction in HCV prevalence over 10 years of 31%, 13%, and 7% assuming background prevalences of 20%, 40%, and 60%, respectively.

Health care–associated transmission. Health care–associated transmission remains an important cause of HCV infection in the United States and globally, estimated to account for 40% of HCV infections worldwide. In countries with high prevalence of chronic HCV infection (ie, >3%), including Egypt, Pakistan, and Mongolia, it is the major transmission mode. In these locales, injections are common and injection practices are difficult to change. In the United States and other countries with low prevalence, health care–associated transmission continues to cause outbreaks. In the United States, 1 to 2 outbreaks are reported every month, typically from outpatient settings such as dialysis, pain management, and oncology clinics. A recent study has shown that exposure to a health care setting is an independent risk factor for acquisition of HCV in people aged 55 years and older in the United States,[4] suggesting that there are ongoing sporadic transmissions that are not revealed in the context of outbreaks.

Other modes of transmission. HCV can also be transmitted through blood contamination of shared devices for nasal insufflation of cocaine. Estimates of HCV-seropositive status among non-IDUs range from 0% to 17%.[5] Mother-to-child transmission from HCV-infected mother to infant occurs in approximately 4% of births and in 25% of births in which the mother is coinfected with HCV and HIV. There is no current recommendation to screen mothers for HCV, because there is no protective intervention that can interrupt transmission.

Heterosexual transmission accounts for 14% of reported cases of acute

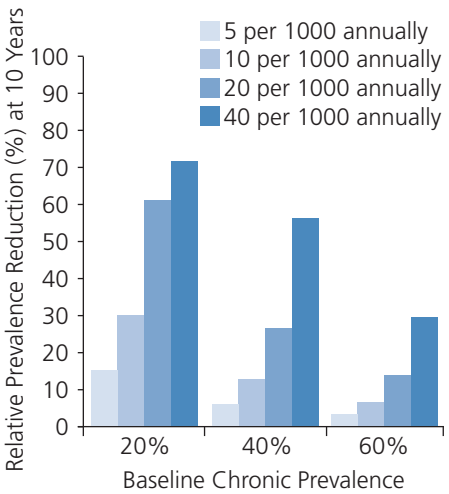

Figure 3. Estimated 10-year relative reduction in hepatitis C virus (HCV) prevalence among injection drug users (IDUs) according to number of HCV-infected IDUs treated annually with assumed sustained virologic response rate of 62.5%. Adapted from Martin et al.[3]

HCV infection in the United States,[6] although transmission has been found to be rare among long-term HCV-serodiscordant couples. HCV infection incidence is high among HIV-infected men who have sex with men (MSM), estimated at 6.08 cases per 1000 person-years.[7] Household contacts of infected persons are at 2-fold increased risk of infection as a result of incidental blood exposure from such items as toothbrushes and razors. Approximately 3% of acute HCV-infection cases in the United States occur in health care workers as a result of occupational exposure.[6]

HCV Screening

Since 1998, CDC has recommended HCV screening based on risk factors, including any history of injecting illegal drugs; receipt of clotting factors before 1987; receipt of blood or organ transplants before July 1992; history of chronic dialysis; evidence of liver disease (eg, persistently abnormal levels of alanine aminotransferase); and having HIV infection. Children born to HCV-infected mothers also are at risk, along with health-care, emergency medical, and public safety workers with needlestick, sharp, or mucosal exposure to HCV-positive blood.

Risk-based strategies to reduce transmission continue to be important, and attempts to refine such strategies are in progress. Some issues being considered include how often IDUs should be tested to detect recent or recurrent infection, and whether sexual contacts of HIV-infected MSM should be screened. However, risk-based strategies are insufficient to satisfactorily identify all HCV-infected persons and thereby potentially reduce transmission. Inherent barriers to a risk-based approach to testing include limitations in physician knowledge and experience, patient concerns about stigma, and poor patient recall of long-past risk behaviors. Further, individuals may not be aware that they are at risk of exposure to HCV in medical or other settings. Overall, it has been estimated that 45% to 85% of HCV-infected persons in the United States are unaware of their infection status.[8-10]

One striking example of the inadequacy of risk-based testing is provided by a study in 170 HCV-infected people identified through the 2001-2008 National Health and Nutrition Examination Survey (NHANES). Of these persons, 51% were unaware of their infection status prior to being tested in the survey. Among those who were aware of their infection status before the survey, the reasons for prior HCV testing were routine physical or blood test in 46%, symptoms of hepatitis in 16%, blood donation in 10%, and HCV risk factors in 4%.[11]

The Good News and the Bad News: HCV Can Be Cured, But Most Infected Patients Are Not in Care

The advent of DAAs brings promise of increasing cure rates with shorter treatment durations and reduced rates of serious adverse events in HCV-infected patients. Regimens consisting of all oral agents have been found to produce high clearance rates, sometimes exceeding 90%, with 12 weeks of treatment, and more than 20 investigational drugs currently are in phase II or III trials. However, the benefits of such improved treatment in reducing the burden of HCV disease cannot be realized if infected persons are not brought into care. Testing is the link that will identify infected people. Extra effort will be needed to bring infected persons into care.

To increase identification of HCV-infected individuals in the United States, the first step CDC recommends is to implement a 1-time test for all persons born between 1945 and 1965. This birth cohort has an infection prevalence of 3%, approximately 5 times greater than the prevalence among other adults. An evidence-based review of the strategy of testing this population and linking infected people to care indicates that treatment-related clearance of infection would reduce the risk of HCC by 70% and lower the risk of all-cause mortality by 50%. The NHANES survey mentioned above found that 50% to 60% of HCV-infected persons had at least 2 alcoholic drinks per day. A clinician-directed intervention on alcohol use as part of the care of infected patients identified through 1-time testing was estimated to decrease alcohol use by more than 38% over 1 year of follow-up. Harms of the 1-time testing strategy would include exposure to HCV treatment that is not effective and potentially serious but reversible adverse events.

The potential health impact of this birth cohort strategy is summarized in Table 1.[12] The model initially included only the impact of effective treatment with peginterferon alfa and ribavirin,

Table 1. Estimated Health Impact of Testing the 1945 to 1965 Birth Cohort for Hepatitis C Virus (HCV)

	Birth Cohort Testing With Therapy	
Outcome	**Peginterferon alfa/ribavirin**	**Peginterferon alfa/ribavirin with telaprevir**
Additional identified cases	809,000	809,000
Cirrhosis cases averted	138,000	203,000
Decompensated cirrhosis cases averted	50,000	74,000
Hepatocellular carcinoma cases averted	32,000	47,000
Transplants averted	11,000	15,000
Deaths from HCV averted	82,000	121,000
Medical costs averted	$1.5 billion	$2.5 billion
Costs per QALY gained	$15,700	$35,000

QALY indicates quality-adjusted life-year. Adapted from Rein DB et al.[12]

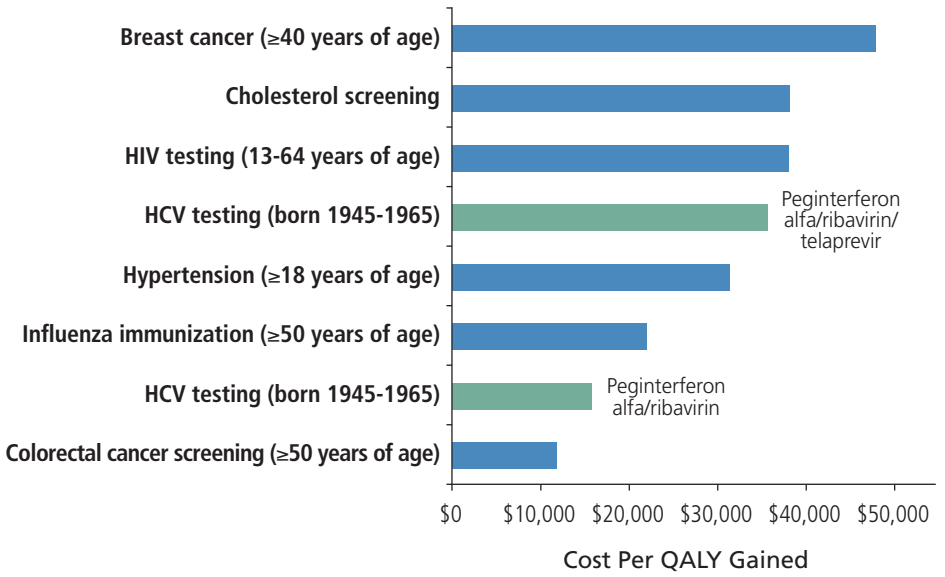

Figure 4. Comparison of cost-effectiveness of hepatitis C virus (HCV) strategy compared with other routine preventive services. QALY indicates quality-adjusted life-year. Adapted from http://www.prevent.org/National-Commission-on-Prevention-Priorities/Rankings-of-Preventive-Services-for-the-US-Population.aspx. Accessed December 4, 2012.

because that therapy was the only US Food and Drug Administration (FDA)-approved treatment at the time the analysis was started. Modeling that included the effect of the DAA telaprevir was subsequently performed when the drug was approved for use in combination with peginterferon alfa and ribavirin. As shown, it is estimated that full implementation of the strategy could identify 809,000 additional cases of HCV infection. Treatment that included telaprevir could avoid 203,000 cases of cirrhosis, 74,000 cases of decompensated cirrhosis, 47% of cases of HCC, 15,000 liver transplants, and 121,000 deaths. HCV infection is associated with substantial financial costs, with patients having 3-fold more disability days (1.36 vs 0.34 days) than other employees[13] and much higher annual health care costs ($21,000 vs $5500 for others).[14] With implementation of the birth cohort strategy, a total of $2.5 billion in medical costs could be averted. The costs per quality-adjusted life-year (QALY) gained are estimated to be $15,700 with peginterferon alfa and ribavirin treatment, and $35,700 with treatment including telaprevir. These estimates compare well with estimates for other interventions considered to be good medical practice in the United States (Figure 4).

Based on such analyses, CDC has added a new recommendation to the existing risk-based testing recommendations, as follows:

- Adults born during 1945 through 1965 should receive 1-time testing for HCV without prior ascertainment of HCV risk factor (*strong recommendation, moderate quality of evidence*).
- All persons with identified HCV infection should receive a brief alcohol screening and intervention as appropriate, followed by referral to appropriate care and treatment services for HCV infection and related conditions as indicated (*strong recommendation, moderate quality of evidence*).

Control and Elimination of HCV Transmission and Disease

HCV presents numerous epidemiologic challenges. HCV transmission continues to occur, with incidence appearing to be increasing in some US populations, such as young people living in the Northeast and Midwest, and perhaps the Appalachian region. The burden of chronic infection and related disease is large, with the large population of people living with HCV becoming increasingly ill with HCV-related liver disease. At a time when anti-HCV therapy is improving, many if not most persons living with HCV infection remain undiagnosed and unaware of their infection status.

HCV infection is a health disparity for persons born during 1945 through 1965. The fact that most of the infected individuals in this cohort do not know their infection status provides a strong motivation for implementation of the CDC recommendations regarding testing and linkage to care. The goal is the control and eventual elimination of HCV transmission and disease. Achieving this goal requires comprehensive strategies to prevent transmission and to prevent consequences of chronic infection. Risk-based prevention strategies are necessary to detect and prevent new infections, whereas 1-time testing for the 1945-to-1965 birth cohort reduces morbidity and mortality among those infected.

New HCV therapies also promise to be powerful prevention tools in reducing transmission of new infections and the consequences of chronic HCV infection. However, HCV testing and linkage to care must improve if the health gains that are anticipated with the new therapies are to be realized. To achieve our goals, collaborations are essential among public health agencies, clinical care providers, laboratories, and payers to improve HCV testing, prevention, care, and treatment.

Presented by Dr Ward in October 2012. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Ward in March 2013.

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Cases on the Web

NEW Preventing Anal Cancer in HIV-Infected Men and Women

Timothy Wilkin, MD, MPH
CME Credit Available: 1.50 *AMA PRA Category 1 Credits*™
Level: Advanced

Anal cancer is an increasingly common cancer among HIV-infected adults. High-grade anal intraepithelial neoplasia, for which there are several treatment options, can be diagnosed using anal cytology and high-resolution anoscopy with biopsies.

NEW Chronic Obstructive Pulmonary Disease in the HIV-Infected Patient

Daniel K. Shirley, MD, and Robert J. Kaner, MD
CME Credit Available: 1.50 *AMA PRA Category 1 Credits*™
Level: Advanced

Smoking prevalence is increased in the HIV-infected population, and studies suggest an increased susceptibility to chronic obstructive pulmonary disease (COPD) in this group. HIV primary care practitioners must be knowledgeable about diagnosis and management of COPD.

These activities have been approved for *AMA PRA Category 1 Credit.*™

COMING SOON

Look for these new *Cases on the Web* activities.

March: Neurologic Issues in Advanced HIV Infection

Scott L. Letendre, MD

Neurocognitive problems are common in people with HIV, even those on successful antiretroviral therapy. In addition to HIV, several other common conditions can injure the brain, making diagnosis and management complex.

www.iasusa.org/cow

April: Transitioning HIV-Infected Youth Into More Mature Care Settings Case 2: Transition of Adults from Adolescent to Adult Care

Aracelis D. Fernandez, MD, and Stephen Stafford, BA

As young HIV-infected patients age, they will transition to medical and psychosocial services at adult care settings. This involves an adjustment to new practitioners and surroundings and to a health care approach that is reliant on a young person's capacity for self-care.

Other Currently Available *Cases on the Web*

Primary Care Issues in HIV Infection

Howard Libman, MD

Progressive Multifocal Leukoencephalopathy in HIV Infection

David B. Clifford, MD

The Use of Hepatitis C Virus (HCV) Protease Inhibitors in HIV/HCV-Coinfected Patients

Jennifer C. Lin, MD, and David L. Wyles, MD

Management of Chronic Hepatitis C Virus Infection in Advanced Liver Disease

Kenneth E. Sherman, MD, PhD, and Syed Hussain, MD

Drug Interactions With Medications for Treating Hepatitis C Virus Infection

John J. Faragon, PharmD, BCPS

HIV and Pain

Jessica S. Merlin, MD, MBA, and Rodney Tucker, MD, MMM

Review

The Role of Palliative Care in the Current HIV Treatment Era in Developed Countries CME

Jessica S. Merlin, MD, MBA, Rodney O. Tucker, MD, MMM, Michael S. Saag, MD, Peter A. Selwyn, MD, MPH

The goal of palliative care is to minimize and prevent suffering and maximize physical function and quality of life in patients with serious illness. In the early years of the AIDS epidemic in developed countries, prognosis was poor and palliative care was often inseparable from HIV care. Despite the advent of effective antiretroviral therapy and its availability in developed countries, patients with HIV disease still present many palliative care challenges and opportunities. The cases of 3 HIV-infected patients who embody these challenges will be presented in this article: an older patient with numerous medical comorbidities, chronic pain, and severely impaired physical function; a patient with psychiatric illness and substance abuse, difficulties with adherence to antiretroviral therapy and retention in HIV primary care, and cryptococcal meningitis; and a patient with stable HIV disease and hepatitis C virus–related liver failure. These cases are being presented to stimulate a discussion between HIV and palliative care practitioners about potential areas of clinical and research collaboration.

The goal of palliative care is to alleviate and prevent suffering in patients with serious illness. Early in the AIDS epidemic in developed countries, prognosis was universally poor. HIV care and palliative care were seen as one and the same, and HIV practitioners, by necessity, became experts in palliative care. Patients dying with AIDS needed palliative care to help ease their suffering at the end of life; suffering related to pain and other symptoms experienced during the dying process, and eventually, suffering related to toxic antiretroviral medications used in the early treatment era. This era, the pre–potent antiretroviral therapy era, is an era that the field of HIV medicine was glad to leave behind.

The AIDS epidemic has changed dramatically over the past 20 years. With the introduction of effective antiretroviral therapy and its widespread uptake in developed countries, the epidemic has matured. By 2015, 50% of patients with HIV disease in the United States will be older than 50 years.[1,2] In addition, patients with HIV disease often have numerous comorbidities, such as cardiovascular, renal, or liver disease, and non–AIDS-defining malignancies. This has been described as a process of "accelerated aging."[3] The combination of a "graying" epidemic and multimorbidity likely contributes to the high prevalence of pain and symptoms still seen in patients with HIV disease. Estimates of pain occurrence in the current HIV treatment era in studies from the United States range from 39% to 55%.[4-13] Physical symptoms such as nausea and fatigue and psychological symptoms such as depressed mood and anxiety are also common.[7,9-11,13-16] Data from the pre–potent antiretroviral treatment era suggest that pain is underrecognized and undertreated.[17-19] Adding to this complexity, psychiatric illness and substance abuse are common in HIV-infected patients.[20-22] All of this is compounded by an aging population, in which the complications of HIV as a chronic disease now intersect with the added challenges of geriatric care. These myriad issues lead to growing clinical complexity and impaired quality of life for HIV-infected patients.

Despite advances in therapeutics, patients with HIV infection still die, even in settings in which antiretroviral therapy is widely available. Deaths attributable to AIDS in an era of antiretroviral therapy have shifted "from fate to tragedy," often relating to late diagnosis or failures in adherence to antiretroviral therapy or retention in HIV primary care.[23] Today, AIDS-related deaths account for less than half of all deaths in patients with HIV disease; the remainder are primarily due to other comorbidities such as liver disease and non–AIDS-defining malignancies.[24] Many HIV-infected patients are now being cared for by a generation of physicians who did not experience the epidemic of suffering, dying, and death in the pre–potent treatment era, and who may not be

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as attuned to the palliative aspects of HIV disease.

Palliative care as a medical specialty has also evolved over the past 20 years. It emerged from the hospice movement and is often employed near the end of life. However, palliative care has been increasingly understood as an approach to minimize and prevent suffering while maximizing physical function in the face of serious illness, irrespective of stage of illness or prognosis (Figure).[25,26] Palliative care has been successfully integrated in the early stages of illness in patients with complex diseases such as heart failure, chronic obstructive pulmonary disease (COPD), and cancer.[27-30]

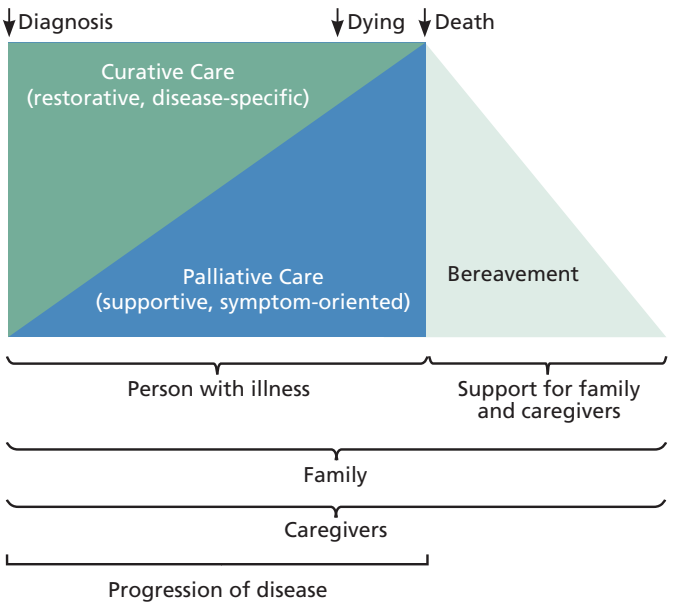

Figure. Palliative care's place in the course of illness. Adapted from World Health Organization.[53]

Palliative care has recently been recognized as a medical specialty in the United States, requiring fellowship training and board certification for physicians who practice in this area. The palliative care skill set includes pain and symptom management and communication about physical, emotional, psychosocial, and spiritual suffering in the context of serious illness. In particular, palliative care specialists have specific expertise in communicating about goals of care. Common goals of care include functional improvement, comfort, and caregiver support and are considered an essential part of discussions with patients with serious illness.[31]

Palliative care is, by definition, interdisciplinary in nature. Physicians, nurses, psychologists, social workers, chaplains, physical and massage therapists, and counselors with special expertise and training in palliative care work together with patients' primary practitioners to help patients who are suffering achieve their care goals. When appropriate, palliative care can also help patients whose health is rapidly declining, or who are nearing the end of life.

Therefore, palliative care is a natural fit to address suffering and maximize function and quality of life for patients living with HIV disease, and for patients with HIV disease who are nearing the end of life.[32] Unfortunately, palliative care for patients with HIV disease in the current treatment era in developed countries has received little attention in the HIV literature or at national and international HIV conferences. This is a missed opportunity. Inpatient and ambulatory palliative care programs are growing rapidly, with more than 60% of US hospitals now providing a palliative care team.[33] HIV clinicians have the opportunity to collaborate with and learn from their palliative care colleagues, to integrate palliative care with disease-specific care for patients with HIV in order to improve their quality of life and HIV-related clinical outcomes. Three cases are presented that illustrate opportunities for integration of palliative care with disease-specific care for patients with HIV throughout the course of their illness. The intent is to stimulate a dialogue between HIV and palliative care practitioners and researchers and to challenge us to consider novel ways to reduce patient suffering while improving their physical function and quality of life.

Cases

Case 1: Aging With HIV

Mr A, a 65-year-old white man, was diagnosed with HIV infection in 1996 during an episode of *Pneumocystis jiroveci* pneumonia. Mr A has a history of good adherence to antiretroviral therapy and retention in HIV primary care. He is currently taking a regimen of emtricitabine, tenofovir, and ritonavir-boosted darunavir, his CD4+ count is 350 cells/μL, and his viral load is undetectable. Over the past 10 years, Mr A has developed several comorbidities. He has diabetes, requiring oral hypoglycemic therapy and insulin. Although he is not overweight, he has central adiposity, and his total cholesterol and triglycerides are elevated. He also has peripheral neuropathy, which may be secondary to a combination of early treatment with stavudine, diabetes, and HIV itself. His neuropathy improved somewhat after initiation of gabapentin but still affects his quality of life. Last year, he began to have hip pain and was diagnosed with bilateral severe hip osteonecrosis. The pain has severely limited Mr A's mobility and he is unable to participate in activities that he previously enjoyed, such as working in his garden or playing with his nieces. While undergoing an evaluation for a bilateral total hip replacement, he had an episode of chest pain and a positive stress test, resulting in a cardiac catheterization and stent placement. Over the past few years, Mr A has also begun to appear more frail; he is thinner, has less muscle mass, has a slow gait, and has begun to show signs of cognitive decline.

Mr A lives with his 85-year-old mother and has become increasingly dependent on her for some activities of daily living, such as grocery

shopping and other errands. She has cardiovascular disease and suffers from arthritis, which impairs her mobility. Mr A notes that his mother's health has been declining over the past year, and notably, they share many of the same comorbidities.

Commentary

This case illustrates the numerous challenges that may be faced when caring for aging HIV "survivors." At this point in Mr A's illness trajectory, diabetes and cardiovascular disease have surpassed HIV infection itself as drivers of functional impairment. An HIV practitioner, seeing this patient in a 15- to 30-minute office visit, is likely to focus on the biggest threats to Mr A's health: his cardiovascular risk factors and glycemic control. However, there are other pressing issues that must be addressed, including Mr A's disabling pain, his increasingly challenging family environment, his cognitive decline, and possibly his mood.

Research on the impact of chronic pain in patients with HIV disease and the approaches to its management in the current treatment era is limited. There is some evidence that pain impacts retention, adherence, virologic suppression, and physical function in HIV-infected patients.[10,12,34,35] The goal of successful chronic pain management is to restore physical function. This involves a combination of pharmacologic management and the use of psychologic-based therapeutic techniques. In this case, Mr A's peripheral neuropathy is only somewhat improved with gabapentin. Numerous other pharmacologic agents (Table 1), in addition to cognitive behavioral therapy and supportive psychotherapy,[36] are effective in the treatment of this painful disorder. In addition, although not a factor in this case, psychiatric illnesses such as mood disorders and substance abuse must be addressed when present, as these often impact the patient's pain and response to therapy.[37]

Mr A's chronic pain and declining health impact his relationship with his mother, who is also ailing. Mr A may wonder what will happen if his mother can no longer take care of him, or of herself. Mr A's mother may be experiencing a high degree of caregiver burden from caring for an adult child who is declining.

Consultation with a palliative care specialist could assist Mr A with the activities and issues that are most important to him. It is becoming more common for palliative care providers to see patients with chronic pain in the ambulatory setting.[38] A palliative care approach to this patient's chronic pain could include pharmacologic management, including opioids and drugs specifically targeted at peripheral neuropathy (ie, gabapentin, pregabalin, or other anticonvulsants); setting realistic functional goals with the patient; using advanced therapeutic techniques such as cognitive behavioral therapy and motivational interviewing to help him achieve his goals; assessing the patient for cognitive decline and mood disorders such as depression and anxiety; and testing for hypogonadism, given the patient's frailty and declining muscle mass. Addressing the patient's declining health, planning for the future, treating his comorbidities and increasing frailty, and anticipating advanced care planning for an ailing parent are all part of the palliative care skill set.

Additionally, palliative care is provided in the context of an interdisciplinary approach, which includes nurs-

Table 1. Agents Used in the Treatment of Peripheral Neuropathy in HIV-Infected Patients

Agent	Comments
Gabapentin[a]	In a randomized controlled trial of gabapentin vs placebo in 26 HIV-infected patients, 44% of subjects reported improvement in neuropathic pain and 48% reported improvement in sleep in the gabapentin group, and no improvements were reported in the placebo group.[44]
Pregabalin	A randomized controlled trial of pregabalin vs placebo in 302 HIV-infected patients showed lack of superiority of pregabalin.[45] However, based on its similarity to gabapentin, and its ease of administration and superior tolerability, it is often prescribed for the treatment of peripheral neuropathy.
Amitriptyline	Randomized trials of amitriptyline, mexiletine, or placebo[46] and a 2 x 2 factorial design of amitriptyline and acupuncture[47] found no difference between amitriptyline and placebo. However, due to its efficacy in other populations (eg, diabetic neuropathy), amitriptyline and other tricyclic antidepressants are often used to treat neuropathy in HIV-infected patients.
Capsaicin[a]	Two similarly designed randomized controlled trials in which high-dose capsaicin (8%) was compared with a low-dose control (0.04%) demonstrated efficacy. Analysis of combined data from both trials showed an improvement of 27% with the high dose vs 16% with the low dose (n = 239 and n = 100, respectively).[48]
Lidocaine	A randomized, controlled, crossover study of topical lidocaine in 64 participants found it to be no more effective than placebo in HIV-infected patients with peripheral neuropathy.[49]
Opioids	There are no studies of opioids in HIV-infected patients with peripheral neuropathy. However, opioids are commonly used in the treatment of chronic nonmalignant pain and, in particular, have been shown to have at least some efficacy in the treatment of neuropathic pain in non–HIV-infected patients.[50] They are sometimes used in the management of peripheral neuropathy in HIV-infected patients.

Based on the literature for diabetic neuropathy, duloxetine or valproic acid may be considered for second-line management of peripheral neuropathy in HIV-infected patients.

[a]Proven efficacy for HIV peripheral neuropathy in at least 1 randomized controlled trial. Compiled from Hahn et al,[44] Simpson et al,[45] Kieburtz et al,[46] Shlay et al,[47] Brown et al,[48] Estanislao et al,[49] and Eisenberg et al.[50]

es, social workers, and chaplains with palliative care training or expertise. The focus of the palliative care team's efforts is not only on the patient but on the patient's entire family or support system. In the case of Mr A, team members could be involved in a variety of ways, including emotional and spiritual support to him and his mother, which is an often neglected but important part of decision making for patients with life-threatening illness,[39] and identifying community resources such as meal preparation programs or caregiver support.

Case 2: Retention and Adherence

Ms B is a 22-year-old African American woman who was diagnosed with HIV infection during a pregnancy 5 years ago and placed on antiretroviral therapy. She gave birth to a healthy, HIV-seronegative girl. Her CD4+ count at antiretroviral therapy initiation was 200 cells/mL and was 300 cells/mL with an undetectable viral load at the time she gave birth. She was encouraged to continue on antiretroviral therapy and was connected to a Ryan White HIV/AIDS Program clinic to receive ongoing HIV care. Ms B has suffered from addiction to cocaine since the age of 16 years. During her pregnancy, she lived in a recovery house and was able to deliver her baby cocaine-free. However, after giving birth, she suffered from depression and relapsed. Her daughter was removed from her care by social services and taken to live with the patient's parents. Despite numerous calls from the clinic social workers and other staff trying to locate her, Ms B disappeared from the clinic. When she reappeared a year later, it was at a dual diagnosis unit where she was hospitalized for depression and cocaine relapse. After discharge, she was referred back to the Ryan White clinic. Laboratory samples were drawn, and a 1-month follow-up visit to discuss reinitiation of antiretroviral therapy was scheduled. Ms B missed that visit and clinic staff were later notified that she was in the hospital again. She had been found unresponsive in a local park; her urine tested positive for cocaine, and a lumbar puncture revealed an opening pressure of 30 cm and a white blood cell count of 100/μL. Her cerebrospinal fluid tested positive for cryptococcal antigen and an India ink stain showed yeast forms. She was hospitalized for 2 weeks, during which time she suffered from severe headaches, nausea, and vomiting. She received therapy with liposomal amphotericin and flucytosine and daily lumbar punctures. She was discharged with a prescription for fluconazole and an appointment to see her HIV care practitioner in 1 month to initiate antiretroviral therapy. She was readmitted after only 2 weeks, once again with a urine drug screen that tested positive for cocaine, a full bottle of fluconazole in her pocket, and a relapse of cryptococcal meningitis.

Commentary

This is an all too common scenario and is likely to cause distress not only for the patient and her family but for the medical team involved in the patient's care. This patient is young and has the potential to be relatively healthy. Unfortunately, this patient has experienced a high burden of illness secondary to depression and substance abuse, which have impacted key health behaviors: retention in HIV primary care and adherence to antiretroviral therapy. She now has cryptococcal meningitis, which if not treated properly is universally fatal. Her prognosis could be excellent, but given her psychiatric and substance abuse comorbidities is likely poor.

Ms B's suffering is multifaceted. In palliative care, this is often conceptualized as "total pain," which includes suffering that is not only physical but also psychologic, social, emotional, and spiritual.[40] She has a high burden of physical pain and nausea, which, regardless of their cause or the fact that they could have been prevented, can be treated with careful selection of analgesics and antiemetics (Table 2). The assessment and management of symptoms in a patient with altered mental status may be particularly complex but can be achieved. The patient's

Table 2. Mechanisms and Locations of Action of Common Antiemetic Therapies

Etiology	Pathophysiology	Therapy
Brain metastases, meningeal irritation	Increased intracranial pressure	Steroids
Movement	Vestibular stimulation	Anti-acetylcholine (scopolamine)
Anxiety	Cortical	Anxiolytics (benzodiazepines)
Medications (chemotherapy, opioids)	CTZ, vestibular stimulation	Antidopaminergics (haloperidol, metoclopramide), antihistamines (diphenhydramine, meclizine), serotonin antagonists (ondansetron), anti-acetylcholine
Motility (opioids, ileus, other medications)	Gastrointestinal	Prokinetic agents (metoclopramide), stimulant laxatives (sennosides)
Mechanical obstruction	Constipation, tumor, stricture	Manage constipation, surgery when appropriate, steroids, inhibit secretions with octreotide
Metabolic (hypercalcemia, hyponatremia, hepatic or renal failure)	CTZ	Antidopaminergics, antihistamines, fluids, steroids

CTZ indicates chemoreceptor trigger zone (medulla). Adapted from Glare et al[51] and International Palliative Care Resource Center.[52]

psychiatric illness and substance abuse are also likely to be contributing to her suffering and must be directly addressed; given the barriers to accessing mental health services in the United States, it is often difficult to address these issues. Ms B and her family may also experience a high degree of emotional and existential suffering, and even grief, over how their lives have been changed so dramatically by Ms B's illness.

These are complex issues that may be difficult to address in the context of an inpatient hospital stay. Two central themes of the palliative care approach are identifying the patient's and the family's goals of care, and identifying and treating their suffering, not only physical but spiritual, emotional, and psychosocial. This approach is especially well-suited to situations like Ms B's, which are both medically and socially complex. Communicating with patients about goals of care and suffering under such complex circumstances is often challenging; palliative care interdisciplinary team members must be highly skilled communicators. By understanding the patient's and family's goals, the palliative care team can help guide the patient, family, and other clinicians through complex medical decision making.

It is often necessary to call on psychiatric and addiction specialist colleagues to collaborate in cases when mental illness itself has become a barrier to effective HIV treatment. Regardless of the patient's goals of care, treatment of psychiatric illness and addiction as core causes of suffering is essential and must not be overlooked.

Case 3: Liver Failure in an HIV-Infected Patient

Mr D is a 55-year-old white man who was infected with HIV in his 30s when he injected heroin. He was diagnosed with HIV in 2002 and had a CD4+ count of 600 cells/μL. His hepatitis C virus (HCV) antibody test was also positive, with a viral load of 1 million IU/mL. Because of bouts of depression and alcohol abuse, he was deemed to be a poor candidate for HCV treatment with peginterferon alfa and ribavirin and was not started on antiretroviral therapy owing to concerns about adherence. He was observed off antiretroviral therapy until 2009, when his CD4+ cell count was 300/μL, and his HCV viral load was 2 million IU/mL. His laboratory test results were unremarkable, except for a platelet count of 90/μL and an albumin level of 3 g/dL. At that time, he also had a liver ultrasound, which showed results consistent with cirrhosis. Mr D was started on antiretroviral therapy with emtricitabine, tenofovir, and efavirenz for his HIV infection, but due to his advanced liver disease, no HCV therapy was initiated. Over the subsequent 3 years, Mr D developed decompensated cirrhosis. Most troubling was the detection of large-volume ascites that caused the patient abdominal pain and shortness of breath, and hepatic encephalopathy, resulting in numerous hospital admissions and difficulty with his activities of daily living. Mr D also admits to drinking alcohol up until 3 months before his most recent visit and therefore is not a candidate for liver transplant. Mr D is estranged from his wife, whom clinic staff have tried unsuccessfully to locate. He has no other family and does not have a health care proxy.

Commentary

Cirrhosis leading to liver failure is the second most common cause of non–AIDS-related comorbidity and death in patients infected with HIV.[41,42] This patient is not a transplant candidate, because of his alcohol use, and his decompensated cirrhosis and poor functional status make survival to the point of transplantation unlikely. This patient's prognosis is likely a life expectancy of only a few months. As with many patients in this type of situation, Mr D's HIV infection is well controlled, whereas his HCV infection is the primary driver of morbidity and ultimately mortality.

Palliative care involvement, during one of Mr D's many hospital admissions or in the outpatient setting, could be beneficial in several ways. Mr D's symptom burden is high. The use of pharmacologic approaches to relieve his shortness of breath, such as low-dose opioids or benzodiazepines, is challenging for patients with liver disease but achievable with close monitoring. The addition of nonpharmacologic measures, such as forced oxygen treatment or a fan, yoga to help the patient with positioning, relaxation therapy, cognitive behavioral therapies, and paracentesis or peritoneal drain placement, may prove helpful. Addressing his symptoms may help the patient to focus on the things he wants to do during the last stage of his life, such as saying goodbye to the people who are close to him, addressing any outstanding financial issues, and achieving existential or spiritual closure.

Mr D has had bouts of depression and, until very recently, was actively drinking alcohol. Mood disorders and addiction are often ongoing sources of suffering for patients and their families near the end of life. Therefore, it is important to assess these issues, recognizing that the way they should be addressed may be different for patients who have a life-limiting illness than for those who do not; eg, engaging in recovery may not be feasible given the severity of illness; if life expectancy is very short, then a selective serotonin reuptake inhibitor may not be practical; and stimulants like methylphenidate may be used.[43] The interdisciplinary palliative care team, in collaboration with psychiatric and addiction specialists when appropriate, can help address the sources of suffering during the last phase of Mr D's life.

Identifying a health care proxy for patients with serious medical illness is extremely important, especially for patients where no "natural proxy" (ie, easily identifiable next of kin such as a spouse or partner) exists. Mr D should discuss with his proxy his medical condition and what his wishes might be should his condition worsen. The question of artificial nutrition and hydration (eg, a feeding tube) may arise, since Mr D's worsening condition will likely lead to an inability to swallow medications, including lactulose, or eat. The risks and benefits of such

interventions in dying patients must be carefully considered. The medical team should explore whether Mr D would like a team member to be present for his conversation with his health care proxy to assist with communication about these difficult issues. Many patients at the end of life also wish to communicate final thoughts with their families, such as "please forgive me," "I forgive you," "thank you," "I love you," and sometimes, "goodbye" (see http://www.thefourthings.org).

Finally, the question of if and when to stop antiretroviral therapy in patients like Mr D who are dying of a comorbidity, or in patients dying with AIDS, is a challenging one. Many factors must be taken into consideration, including pill burden, cost (especially if hospice care is being considered, as some hospices cannot afford to continue providing antiretroviral drugs), patient and family preference, adverse effects, and whether there are any remaining potential benefits of the medications.

Summary

Palliative care is a specialty that may be applied to the practice of HIV medicine in the current treatment era. Challenges faced by patients and practitioners, such as aging, multimorbidity, complex decision making for seriously ill patients with AIDS, and caring for patients with HIV infection who are dying of causes other than HIV, may be aided by a palliative care approach. These cases are meant to prompt discussion between HIV and palliative care practitioners about potential areas of clinical and research collaboration.

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Review

Impact of New Therapeutics for Hepatitis C Virus Infection in Incarcerated Populations

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Inmate populations bear a disproportionate share of the burden of hepatitis C virus (HCV) infection. With more than 90% of prisoners released back to their communities within a few years of sentencing, incarceration can be viewed as an opportunity to provide HCV screening and therapeutic interventions to benefit the individual, reduce the costs of HCV management to the health care system from a societal perspective, and improve overall public health. Although optimal medical management of HCV within prison settings would increase the current cost of correctional health care, it could decrease transmission within the community, reduce overall disease burden, and lower the future societal health care costs associated with end-stage liver disease. Nonetheless, most prison systems treat only a small fraction of infected inmates. Current and emerging therapeutic agents will cure HCV infection in the vast majority of patients. Mathematical modeling also shows that expanded HCV screening and treatment are cost-effective from the societal perspective. In this article, we will describe appropriate treatment regimens, propose strategies to lessen the burden of these costly HCV therapies on correctional health care systems, and address the challenges of expanded HCV screening in correctional settings.

In the late 1990s, it was estimated that 16% to 41% of prisoners in the United States had evidence of exposure to the hepatitis C virus (HCV), compared with 1.6% in the general population.[1] At that time, 1 of every 3 persons with HCV infection in the country passed through a jail or prison over the course of a year.[1,2] Given the overwhelming number of HCV-infected inmate patients seen by correctional health services, protocol-driven strategies for triaging which inmates to treat and how to treat them gained momentum in the last years of the 20th century.[3] Furthermore, outcomes in correctional systems with standard therapy of peg-interferon alfa plus ribavirin (PEG-IFN/RBV) were comparable to those achieved in the community.[4,5]

Studies have concluded that PEG-IFN/RBV has been cost-effective, with cost per quality-adjusted life-years (QALY) gained less than that of other medical interventions commonly employed in correctional settings, such as hemodialysis.[6] However, only a small percentage of incarcerated individuals with chronic HCV infection have been successfully treated owing to numerous barriers, including low rates of HCV screening in correctional settings, poor access to treatment, and high prevalence of conditions among inmates that are contraindications to PEG-IFN/RBV treatment.[3,4,7,8]

The development pipeline is producing a rush of direct-acting antivirals (DAAs) that will reduce treatment duration in most patients and improve sustained virologic response (SVR) rates. The first 2 HCV protease inhibitors, boceprevir and telaprevir, were approved by the US Food and Drug Administration in 2011. Although DAAs are substantially more effective than PEG-INF/RBV, they also increase costs, from approximately $25,000 per treatment course for 2 drugs to between $50,000 and $75,000 for a 3-drug regimen. In the community, where seroprevalence of HCV is approximately 1.3%, substantially improved efficacy has led third-party payers to embrace DAAs. In correctional systems, however, where HCV seroprevalence has been estimated to be at least 13-fold higher than in the community, costs play a larger role in clinical decision making. Seven years ago, a framework of recommendations for management

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of hepatitis C in correctional care was introduced.[3] The time for revisiting and renovating that framework has come, given the changing epidemiology of the disease, rapid pace of drug development, and high cost of increasingly effective therapies.

Epidemiology of HCV Infection in Inmate Populations

The epidemiology of HCV disease is dynamic rather than static. Although HCV remains highly prevalent among prisoners, there has been a dearth of recent publications updating estimates of the prevalence of HCV among prisoners. Two years ago, a study in New Mexico reported that prevalence among their state prisoners was 40%.[9] In contrast, during the summer of 2011, routine testing in an Atlanta jail found the seroprevalence among detainees to be 7.5%.[10] These variations likely indicate substantial regional differences in the prevalence of injection drug use, particularly for opiates or methamphetamine.[11]

An online survey among all US state correctional department medical directors and health administrators was conducted between November 2011 and February 2012.[12] Responses were received from individuals from all 50 states. Only 12 state prison systems performed systematic HCV antibody screening during 2001 to 2012 and they provided inmate seroprevalence estimates for that period (range, 9.6%-41.1%). Weighting by the size of the systems, the national inmate HCV prevalence in 2006, the midpoint of the observation period, was estimated to be 17.4%.[12] The 1-day population in prison in 2006 was 1.5 million and approximately 260,000 HCV antibody-positive persons were in prison at that point in time.

A previous model estimated that the total number of individuals who spent at least 1 day incarcerated, either in jail or in prison, in 2006 was 10.7 million.[13] The total number of cases of HCV infection represented by all persons who were incarcerated that year was 1.86 million; correctional populations represented approximately a quarter of the US HCV case burden for the year. This proportion represents a decline from the burden estimated in 1997, which was 29.4% to 43.4%. This decline may be explained, in part, by the evolving distribution of HCV, such that a greater proportion of the epidemic is borne by increasingly older populations. Two-thirds of those living with HCV were born between 1945 and 1965.[14] As this birth cohort ages out of the crime-prone years (approximately 20 years to 45 years of age), prisons would be expected to bear a declining share of the HCV epidemic. Nonetheless, correctional populations continue to represent a substantial proportion of the nation's epidemic, and HCV infection remains a major burden within state correctional systems compared with the general population.

Outcomes of HCV Infection With or Without Antiviral Treatment

The high prevalence of HCV infection among inmate populations, along with other significant and highly prevalent cofactors (such as HIV coinfection or alcohol use) has led to an increasing number of cases of end-stage liver disease (ESLD) in correctional facilities.[15] Once ESLD develops, liver transplantation often becomes the only chance for extended survival. One study in the Texas prison system showed that over a given 3.5-year period, 484 patients (131 per 100,000 of all prisoners in Texas incarcerated during any point in the study period) reached ESLD; 89% of these patients had HCV infection. Fifty-eight of these patients with ESLD were within 3 months of needing a liver transplant at the time of evaluation.[15]

Prisoners without cirrhosis or ESLD who are not treated with antiviral therapy during incarceration remain at risk for cirrhosis either in prison or in the years following release. If prisoners with advanced fibrosis or cirrhosis receive treatment and viral eradication results, liver decompensation, hepatocellular carcinoma, and liver transplantation can be reduced by approximately 80%.[16] The avoidance of ESLD as a public health issue for the community as a whole may be the best justification for in-prison HCV treatment.[15]

Experience With Conventional Treatment Behind Bars

Correctional systems have a constitutional obligation to provide adequate health care to inmates, including HCV management. State prison systems and health care practitioners either have proactively developed treatment guidelines or litigation has forced them to address HCV treatment. The obligation to address health issues stems from the US Supreme Court decision in *Estelle v Gamble*, wherein denial of necessary medical care or deliberate indifference to serious medical needs of inmates was established as a violation of the Eighth Amendment: the right to be free of cruel and unusual punishment.[17,18] Subsequent court decisions have refined the definitions of "serious medical need" and "deliberate indifference." The definition of serious medical need has varied but has largely been left to the discretion of physicians (eg, "one that has been diagnosed by a physician as mandating treatment") or in the hands of laypeople (eg, "one that is so obvious that even a layperson would easily recognize the necessity for a doctor's attention").[19-21] "Deliberate indifference" requires that the medical practitioner or custody employee knew of the need for medical care and that he or she delayed or refused to provide proper treatment.[20,22,23] Notably, deliberate indifference has been determined in cases in which practitioners chose an "easier and less efficacious treatment."[17,24-26] A Rhode Island inmate recently received a liver transplant while incarcerated based on the *Estelle v Gamble* decision.[27] Other states may feel obliged to follow the lead of Rhode Island in the future. The Federal Bureau of Prisons, which often leads in the development of clinical policies, has developed guidelines for transplantation services.

Current correctional system guidelines include expected remaining duration of stay as a major factor in treat-

ment decisions for medical problems, including HCV infection. In addition to the expected length of stay, the responsibility for a correctional system to undertake a medical intervention depends on the urgency of existing medical conditions, medical necessity, and the probability of treatment success.[26] For less urgent conditions, the institution's obligation depends on whether addressing them can wait until the inmate returns to the community. In a disease such as HCV, in which pathology may take decades to develop, treatment is not urgent for the short-term inmate.[3] Conversely, with an extended incarceration, correctional systems must address a broader range of medical issues.

Although a short delay in initiating HCV treatment may have no clinical consequences, extended postponement can eventually become clinically significant because earlier stages of infection are more amenable to cure.[28-30] Given that treatment is presently available in the community to well-insured individuals with access to specialists, the specific expected duration of incarceration also plays a role when deciding whom to treat for HCV. The typical individual leaving prison has limited resources and insurance coverage. Thus, if an inmate does not complete his or her course of therapy before release, accessing continued care after release may present a challenge. For this reason, most prison systems want assurance that therapy, if started, will be completed before release. In rare exceptions, a state may have a safety net of practitioners in community health centers across the state who can continue treatment in the case of early release.[31] However, postrelease treatment is typically unavailable to the indigent, thus to attain a cure, the remaining time in the institution must exceed the expected duration of treatment.[32] Because so many inmates do not have a length of stay sufficient for standard evaluation and conventional, year-long therapy, prisons have treated only the small proportion of patients with sufficiently long stays, those with an expected remaining stay of at least 18 months to 24 months.[3] Nonetheless, treating even this small proportion of patients has thus far been a major cost driver in prison health care systems.

Most prison systems have developed protocol-driven strategies of treating HCV infection in patients without contraindications to PEG-IFN/RBV.[3] The majority permit therapy for genotype 2 or 3 HCV disease without a prior liver biopsy for staging. Patients with genotype 1 HCV disease typically undergo pretreatment liver biopsy and therapy as appropriate (eg, fibrosis greater than Metavir stage 1).[3] Some systems may employ blood tests to predict the degree of fibrosis (using indices such as aspartate transaminase [AST] to platelet ratio); those individuals with normal values are less likely to have substantial fibrosis and might be considered a lower priority for biopsy and treatment. Protocols vary from state to state and many states base their recommendations on clinical practice guidelines available on the Federal Bureau of Prisons website (http://www.bop.gov/news/medresources.jsp). As new therapies emerge, state health care practitioners will have an immediate and ongoing need to update their guidelines.

Newer therapies and evolving standards of care will challenge the exclusion based on length of incarceration. Expected duration of treatment is likely to be reduced with each improvement in therapeutic regimens. Prison systems will remain under no obligation to reverse long-standing, slowly progressive disease in short-term inmates. However, if treatment duration is only a few months, a system that has overlooked an infection for years will have difficulty denying care to the prisoner with sufficient time to complete the new regimen. Anecdotally, jails have also started to consider treatment for inmates with long stays. Depending on how brief the durations of new treatments become, the number of persons who might qualify for treatment could grow substantially, given that length of stay has a negative exponential distribution (Figure); that is, most prisoners have a brief length of stay, and few prisoners have very long stays.[33] Finally, if regimens continue to decrease in duration and simplify in application so that primary care practitioners seeing releasees could oversee treatment, systems may begin to consider strategies that allow initiation of HCV therapy in correctional settings and continuation of care in the community. Access to community health care, provided for under the Patient Protection and Affordable Care Act (PPACA), would be an essential component of such a strategy.

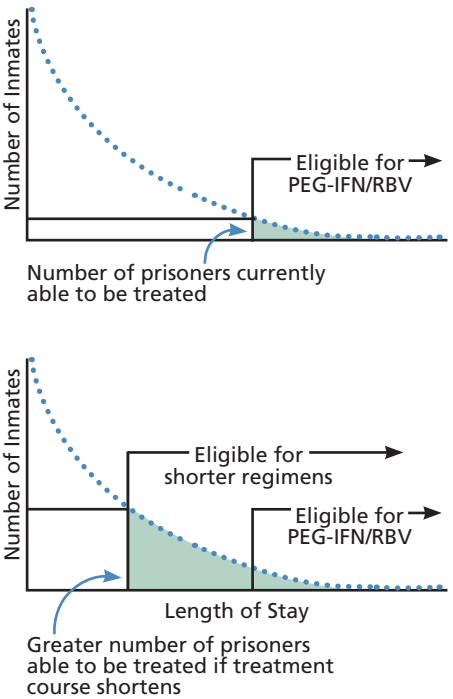

Figure. Impact of length of hepatitis C virus (HCV) treatment and remaining duration of incarceration in prison populations, including prisoners with HCV. The duration of incarceration varies by individual. The frequency of various lengths of stay follows a negative exponential distribution. Many persons have short times remaining before prison release. A few have a very long remaining time to serve. (top) Currently, with a year-long peginterferon alfa plus ribavirin (PEG-IFN/RBV) regimen, only a few prisoners with HCV have sufficient time before release to complete therapy—these are represented by the tail end of the distribution of remaining time to be served. (bottom) Shortening the time to complete HCV treatment by using a novel regimen means that there would be an exponentially greater number of prisoners with HCV who could complete therapy before release.

Considerations for Protease Inhibitor Therapies in Prisons

Adding the first DAAs available, boceprevir and telaprevir, to PEG-IFN/RBV has resulted in dramatically improved outcomes. Nonetheless, the prison environment is not well suited for these agents, because of their unforgiving dosing schedule of every 7 hours to 9 hours and the need for coconsumption of a meal or snack. In prisons, inmates are usually fed en masse and at variable times. Prison nurses usually directly supervise each dose of medication. Groups of inmates queue in "pill lines" on a schedule that is often not coordinated with mealtimes. Protocols have been developed to manage the challenges of synchronizing food intake and medication administration.[34] A favorable consequence of direct observed therapy in prisons is that the regimented system of medication administration may actually lead to greater adherence to treatment in a correctional setting than in the community, which is important when adherence is clearly a substantial factor in successful treatment with triple-drug regimens, or "triple therapy."

Treatment that includes boceprevir or telaprevir, although clearly more effective than dual therapy, adds to cost. A course of therapy with a protease inhibitor added to PEG-IFN/RBV can cost up to $75,000.[35,36] The addition of boceprevir or telaprevir also potentiates cytopenias (particularly anemia), which occur with PEG-IFN/RBV therapy, thus expanding costs to correctional systems via additional laboratory testing and the potential addition of hematopoietic growth factor treatment.

Because of their markedly improved efficacy, however, these agents are cost-effective compared with dual therapy, with an incremental cost-effectiveness ratio of approximately $70,000 per QALY gained.[35] Thus, compared with many other health care interventions commonly provided in the prison setting, triple therapy for HCV provides good value for the money invested.

Advantages and disadvantages of instituting these novel HCV protease inhibitors in correctional settings are summarized in the Table. Potential strategies have been proposed for minimizing costs while preserving efficacy, such as (*a*) pretreatment testing for a genetic polymorphism (interleukin-28 beta subunit [IL-28B]) that predicts response to PEG-IFN/RBV therapy or (*b*) assessment of initial virologic responses with conventional therapy; if a rapid response is achieved, dual therapy may be sufficient. In contrast, if a rapid viral response is not achieved by week 4, then adding a protease inhibitor may improve the chance of viral clearance. Such strategies could allow the use of the less costly dual regimen for persons highly likely to respond to conventional therapy, reserving the more expensive regimens for those who would benefit.[36] On the other hand, proposed strategies that initiate PEG-IFN/RBV only for all patients for the complete course and offer triple therapy to nonresponders are not recommended, because this approach would result in long periods of drug exposure and increase overall costs. These initial DAAs have numerous drug–drug interactions, especially with antiretroviral medications used in the treatment of HIV. Prescribing boceprevir and telaprevir often requires input from a specialist.

Table. Advantages and Disadvantages of Integrating Hepatitis C Virus (HCV) Direct-Acting Antivirals Into Therapy for Inmate Patients With HCV Genotype 1 Infection

Potential Advantages to Adopting Triple-Drug Therapy	Potential Disadvantages of Triple-Drug Therapy
Increased efficacy	Cost
Reduced treatment duration for a subset of patients	Effective, less toxic, and perhaps less expensive therapies may be available in the near future
Standard of care in the community	Additive toxic effects
Opportunity to decrease the epidemic of projected deaths from liver disease	Drug–drug interactions[a]
Avoid overall high costs of advanced liver disease, cancers, and transplants paid for by other publicly funded programs postrelease	Administration schedule: dosing 3 times/day, every 7-9 hours to avoid resistance emergence
Once litigated, prisons will likely be required to provide treatment with triple-drug therapy	

[a]An example of an important drug–drug interaction is off-label use of telaprevir as part of a regimen to treat HIV-infected patients who are taking the antiretroviral drug efavirenz. Telaprevir has been studied at a 50% higher dose in phase II trials to compensate for expected drug interactions, thus increasing the cost of this regimen. Strategies that compare increased telaprevir dose while maintaining efavirenz or that compare standard telaprevir dose while switching antiretroviral drugs may be considered.

Emerging and Future Therapies

Although boceprevir- and telaprevir-containing triple-drug therapy represent the standard of care as of early 2013 and pose a substantial challenge for correctional systems, evolving antiviral regimens in development will eventually supplant the current paradigm. The next paradigm may involve regimens of only oral DAAs, for which pilot studies have demonstrated that SVR can be achieved without PEG-IFN.[37] The first of these emerging therapies may be more complicated and have more adverse effects than previous standards of care. They will likely, in the immediate future, require practitioner expertise and intensive management. As clinical outcomes and medication tolerability improve,

paradigms will be far simpler to apply, thereby broadening the potential pool of practitioners able to treat HCV infection and reducing the costs of patient monitoring. As efficacy improves, the rationale for liver biopsies may lessen as it did in the past for patients with a favorable HCV genotype (ie, genotypes 2 or 3).[38]

The rapid evolution of community-standard HCV care and potential expansion of the pool of individuals eligible for treatment will need to be met by nimble approaches in order to provide care within prison walls. Such approaches will necessitate expansion of HCV-specific knowledge among practitioners, systems to integrate rapidly changing community standards, and the expertise to choose among a rapidly growing arsenal of antiviral drugs with close monitoring to avoid futile therapies. An innovative model known as Project ECHO (Extension of Community Health Outcomes) has resulted in primary care practitioners being informed by specialists through so-called knowledge networks (eg, via teleconferences) and having advice in state-of-the-art HCV therapy delivered. In a setting where access to specialists had been a major barrier, the efforts of Project ECHO resulted in equivalent SVR rates and lower adverse event rates compared with a central specialty clinic.[9,39] Similar systems could be implemented in prison health care settings to allow wider application of the expertise offered by community specialists.

Screening Practices in Correctional Settings

The rationale for screening is to increase access to therapy and thereby reduce future complications of disease. To borrow a concept from HIV epidemiology, eradication of infection can also lead to a reduction of community viral load, meaning individuals engaging in high-risk behavior are less likely to be exposed to HCV. Treatment can thus result in primary prevention.[40]

Historically, practitioners in the community and in prison systems have been advised to perform HCV screening for individuals at high risk, including injection drug users. However, this risk-targeted approach has proved inadequate, as it depends on ascertainment of illegal behavior[41] that prisoners may be unwilling to admit for fear of additional criminal charges. The recently published recommendations from the Centers for Disease Control and Prevention (CDC) to screen all those born between 1945 and 1965, the age group with the highest prevalence of HCV, if followed in correctional settings, may increase the number of persons who are aware of their infection.[42] A recent cost-effectiveness analysis compared survival, quality-adjusted survival, lifetime medical costs, and the incremental cost-effectiveness ratio of birth-cohort screening for HCV and application of the risk-targeted approach for the United States. Compared with risk-targeted screening, birth-cohort screening with linkage to HCV triple therapy has the potential to identify more than 800,000 additional cases of HCV infection and prevent 121,000 HCV-related deaths at an incremental cost-effectiveness ratio of $35,700 per QALY gained.[43] The authors conclude that birth-cohort screening for HCV in primary care settings is cost-effective.

Although these findings inform policy for community-based settings, their implications for prison health care are not clear. Because incarceration is so closely correlated with drug use, routine universal screening in correctional settings may be the most efficient and cost-effective approach for HCV screening. However, if screening is not coupled with either widely available prison-based HCV treatment or excellent care coordination with community-based treatment systems to ensure postrelease linkage to HCV-care, screening in prisons may be ineffectual. Further, because the demographics, comorbidities, and social history of incarcerated individuals differs substantially from those of the cohorts modeled in analyses of community-based HCV screening, published cost-effectiveness estimates may not be generalizable for policy making in prisons.

HCV screening practices in prison settings, as well as their sensitivity and cost-effectiveness have not been well studied. A 2000 survey of state prisons at a facility level found most prison facilities (69% of facilities, holding 88% of US state prisoners) targeted screening based on risk, patient request, or clinical indication and that few (9% of facilities, holding 6% of US state prisoners) had routine screening. Of note, 33% of tests returned positive results with risk-targeted screening, whereas 27% of tests were positive under routine screening.[44] Risk-targeted screening strategies may be missing a substantial number of cases, and the CDC recommends periodic reassessment of the efficacy of risk-based screening.[1] There may be resistance, however, to deploying broader, routine HCV screening in prison systems, because increased case identification would also increase pharmaceutical expenditures in prison health care systems that are already financially strained.[3]

When HCV infection is detected among state prisoners, health service administrators might ask why detection did not occur prior to imprisonment. Earlier detection may have permitted treatment in the community, where federal funding (eg, Medicaid) and private insurance can supplement state resources. When the burden of treatment falls to prisons, the state alone bears the cost of treatment. One possible approach to reduce the burden of treatment costs to prisons may be for public health agencies to partner with jails to institute screening in short-term facilities.[45] Jail and prison populations have similar risk factors for HCV infection. Most jail admissions do not lead to long-term imprisonment and treatment has rarely been considered feasible for short-term inmates. However, testing in jail settings with appropriate links to community settings for evaluation will allow important preventive interventions and treatment at an earlier stage of HCV infection. For the younger populations passing through jail settings, there may be substantial personal and public health benefits, short of the provision of treatment with antiviral drugs when time is

insufficient, by immunizing against hepatitis A and hepatitis B viruses, determining viremic status, and providing harm reduction. Together, these interventions may prevent new infections in individuals testing negative or in those with cleared infections (spontaneous clearance) or may reduce secondary transmission (by narrowing the pool of HCV-infected persons). Thus, from a societal perspective, coordinated HCV screening and treatment among jails, prisons, and the community may enhance the overall integration of care.

Policy Implications of New Therapies for HCV Infection

The structured prison environment may facilitate excellent adherence to demanding therapeutic protocols and administration schedules. As such, the correctional institution can be an effective site to treat and cure HCV-infected patients in a controlled setting, potentially reducing the burden of ESLD—for patients and for health care payers (both public and private)—upon release to the community.[4,5]

Whereas triple therapy has become the standard of care in the community for individuals with genotype 1 HCV infection, the legal obligations of state correctional health care systems will also shift. As described above, Eighth Amendment principles, and interpretations thereof by the federal courts, prohibit deliberate indifference to serious medical need and delay in providing known, effective treatments. It is likely that the judicial system will ultimately require that state correctional health care systems provide HCV treatment that is consistent with current standards of care in the community (except perhaps in cases in which the length of incarceration is so short that delay in treatment until release would not have adverse clinical impact). Because these therapeutic developments directly impact the legal and fiscal obligations of correctional health administration and the public health, prison systems need to create a strategy to deal with a future in which a higher percentage of inmates can tolerate medications and complete treatment prior to release.

The primary strategic challenge, given the limitations of correctional health care and pharmacy budgets, is the high cost of these new drug regimens. Discounted pricing for pharmaceutical drugs is available to other entities caring for low-income populations under federal provisions (Section 340B) of the Public Health Service Act but is not directly available to prisons by regulations of the Health Resources and Services Administration. Long-standing federal statutory exclusions of inmates from Medicaid and Medicare benefits also leave state and local governments without federal funding support. But well-settled law providing a constitutional right to adequate health care for inmates means that with the exception of federal prisoners, the costs of correctional health care fall entirely on local, county, and state budgets. Given the recent estimate that 9.6% to 41.4% of inmates are seropositive for HCV[12] and that approximately 75% of those with a reactive HCV antibody test are viremic, many of these prisoners may be candidates for DAA treatment. Several authors of this paper estimate that if prices are not lowered, expanded HCV screening and access to treatment in their state's prison system could lead to HCV-related medical costs consuming 10% to 40% of prison system pharmacy budgets. This is an enormous strain on a budget that is already burdened by medications required for a host of other comorbidities, such as serious mental illness, heart disease, kidney disease, and HIV infection.

One important consideration crucial to formulating rational policy for HCV treatment in prisons is the external nature of the benefits gained from HCV cure. Viral eradication stops liver fibrosis progression, but the complications of cirrhosis that would have occurred in the absence of HCV treatment may take decades.[39] As a result, correctional systems are asked to pay for HCV therapy, but they likely will not accrue the future benefits of preventing complications of liver disease. Similarly, when prisons do not have adequate resources to provide treatment, the eventual costs of ESLD will fall on Medicaid, Medicare, and private insurers.

Current health care policy reform provides an opportunity to expand access to HCV treatment, but it could also create additional incentives to postpone HCV therapy in prisons and exacerbate the inefficiencies generated by external benefits. Under a key component of the PPACA, nearly all formerly incarcerated adults (aged 19 years to 64 years) could become eligible for Medicaid (or insurance tax credits) at the time of release. States that elect to opt in to this expanded Medicaid eligibility will qualify for generous federal funding, including funds to initially cover 100% and then 90% of all medical costs for these newly eligible enrollees. As a result, the federal government, rather than the state, will pay the majority of HCV treatment and care costs for former inmates who subsequently live in the community. In contrast, inmates who remain incarcerated will not be eligible for Medicaid or Medicare. As a result, their HCV treatment costs will fall entirely within the state department of corrections health care budget.

For some HCV-infected inmates with short sentences and minimal liver fibrosis, deferring treatment to postrelease may be effective and, from the perspective of the state department of corrections, could contain costs. To the extent that those savings are applied to expanding HCV treatment for those with long sentences or advanced liver disease, the PPACA funding could indirectly result in improved HCV outcomes among current and former inmates. If, however, states pursue an overly aggressive strategy of deferring HCV therapy until postrelease to leverage PPACA Medicaid funding and minimize HCV treatment costs in the correctional setting, increased morbidity and mortality could result. Further, the challenges of postrelease linkage are substantial. Without interventions to ensure postrelease follow-up of HCV infection,[31] deferring treatment may result in maintenance of the status quo, in which as few as 6% of HCV-infected persons initiate HCV therapy.[46]

The cost-benefit analysis of providing HCV therapy to inmates, therefore, must take a societal perspective rather than compartmentalize the state department of corrections, state Medicaid program, and federal Medicaid and Medicare budgets. Policy made purely from the perspective of the state department of corrections, or even of the entire state health care budget, will tend to favor deferring HCV therapy until after release, as doing so will shift costs to the federal government. Similarly, policy made entirely from the perspective of the federal Medicaid and Medicare budget will favor immediate HCV treatment, even for patients who have no immediate need for treatment and who could be treated safely and effectively in a community setting. The societal perspective, which recognizes all costs and benefits related to HCV treatment and complications of HCV infection, regardless of where or when they occur, treats HCV disease in a holistic manner and is likely the only perspective from which to formulate efficient HCV policy that minimizes costs and maximizes public health.

Action items for stakeholders in prisoner health care to address the HCV epidemic as novel therapeutics emerge are summarized below.

1. Develop and implement policies that provide for the clinical care of HCV–infected individuals in prisons that parallels the community and that are adaptable to future needs. When treating HCV infection, appropriate treatment, ie, the community standard of care, can be implemented in correctional settings, rather than less efficacious treatment. Resources should be used wisely; if treatment is futile, eg, when a patient has inadequate response to therapy, having systems in place to stop therapy promptly is important. Information on changing aspects of HCV care should be regularly disseminated (eg, via teleconferencing) among correctional practitioners. Expansion of the pool of practitioners with specific knowledge and skills to provide HCV-related care is also needed, and some of this can be accomplished with models like Project ECHO.[9] The design of treatment protocols and delivery systems nimble and flexible enough to be updated to keep apace with the development of new paradigms and inclusive of special populations such as HIV coinfection is another goal. Finally, it will be important to integrate screening for HCV in both jails and prisons, with appropriate systems for follow-up and treatment in the community once inmates are released.

2. Close knowledge gaps. Correctional health officials can help close knowledge gaps among public policy makers by educating them about the availability and efficacy of new HCV treatments, the short-term increased cost burden on correctional health care systems, and the long-term benefits of these treatments in lowering future health care costs and avoiding much more expensive ESLD and liver transplants in the future.

3. Fully ascertain the impact of the PPACA and expansion of Medicaid in the community on prisoner health. Decision making by policy makers about financing the health care costs of HCV–infected inmates and releasees can be planned and aligned with the benefit of a full understanding of the fiscal impact before and after incarceration, as well as new sources of financing under the federal Medicaid expansion option that becomes available to states in January 2014. Today, most affected inmates cannot qualify for Medicaid coverage upon release, even if they have little or no income. Although most releasees may qualify for care at community health centers, the costs of these health center systems fall mainly to practitioners and state-funded safety net programs. Under the PPACA, however, generous federal matching funds will become available to state Medicaid programs that opt in to expanding Medicaid coverage to all adults with low income (ie, income at or below 133% of the federal poverty level after income "disregards" are applied). Because almost all releasees would meet the low-income eligibility criteria, the PPACA Medicaid expansion presents a compelling opportunity for states to substantially improve the coordination of effective postrelease treatment and to provide continuity of care for releasees.

4. Plan now to deliver state-of-the-art HCV care, before litigation. Jurisdictions that have not already done so can engage in strategic planning now for the new resources and funding needed to appropriately screen, treat, and coordinate postrelease community care for inmates with HCV infection. Because the new treatment protocols are now recognized as the community standard of care for affected individuals, well-settled constitutional requirements to provide timely medical treatments to inmates will apply to these new HCV therapies. It may only be a matter of time before lawsuits will result in court decisions ordering provision of these treatments to inmates with and without HIV and HBV coinfection whenever they are clinically indicated and delay would have adverse clinical outcomes.

5. Negotiate discounted pharmacy pricing for novel therapeutics. In light of the known long-term public health benefits and substantial cost savings in the long-term costs of liver disease for the entire health care system, it is important for federal policy makers to reevaluate exclusionary policies relative to discounted pharmacy pricing for state correctional health systems. Current federal regulations governing the pharmacy discount pricing program known as 340B severely limit the capacity to obtain discounted pricing for medications used in correctional health systems, leaving state prison systems to bear the full cost of very expensive therapies. Even if society as a whole would benefit from avoiding treatment of ESLD, currently, there is no incentive for prisons to avert future, society-wide health care costs. Changing federal policy to make 340B discounted pricing available to state correctional facilities would give financial incentives for states to treat early-stage disease.

6. Approach all of HCV management from a societal perspective. Public health policy making can address HCV treatment decisions in a holistic manner, rather than compartmentalizing in-prison and community-based costs of funding the current community standard of care for HCV treatment. It is important that cost-benefit analysis of providing triple-drug therapy to inmates take into account the substantial but downstream long-term benefits gained from HCV cure. Viral eradication stops liver fibrosis progression and the complications of cirrhosis, ESLD, and the need for liver transplants that otherwise would have occurred decades later. When the public health benefits for society and the lower lifetime costs for the whole health care system of appropriate HCV screening and treatment are taken into consideration, the short-term costs to state correctional facilities are more than offset.

7. Determine an agenda for future research. Better data collection is needed to measure disease burden and project costs to both correctional and community health care systems. Only 12 states have recently surveyed their prison system for current seroprevalence. States should consider surveying all state-funded health care populations, including prison populations, to determine prevalence across state-funded programs and to assess downstream fiscal impacts of providing or delaying treatment. Design and funding of interventions that determine the best approaches to integrate HCV care for inmates across the jail, prison, and community settings are necessary. Similarly, the efficacy of newer treatment regimens and unique strategies for addressing HCV infection within prison walls can be studied to understand barriers to care within prison systems and compared with community-based outcomes. Finally, mathematical modeling can effectively describe the specific impact of screening and treatment of HCV–infected individuals in prisons on societal disease burden and costs, including lowering liver disease burden and the community viral load of HCV.

New therapeutics for HCV are expected to become available at a quickened pace. Incarcerated individuals infected with HCV stand to benefit from treatments with better efficacy. These developments can be an opportunity to rethink the financing of correctional health care.

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