

# Topics in Antiviral Medicine™

A publication of the IAS–USA

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Metabolic Complications of HIV Infection and Its Therapies 651

*Edgar Turner Overton, MD*

*Atherosclerotic Heart Disease • Frailty • Obesity and Inflammation*

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Antiretroviral Therapy and the Kidney 655

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*Acute Kidney Injury • Chronic Kidney Disease*

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Non–AIDS-Defining Cancers 660

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*Increase in Non–AIDS-Defining Cancers • Higher Cancer Mortality in HIV-Infected Patients • Pathogenesis of NADCs • Cancer Screening • Cancer Prevention*

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## Special Contribution

2014 Update of the Drug Resistance Mutations in HIV-1 642

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

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# Topics in Antiviral Medicine™

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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 2.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This continuing medical education (CME) activity is offered from July 30, 2014, to July 30, 2015. 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.

## Overview

- CME credits available: 2.0 *AMA PRA Category 1 Credits™*
- Release date: July 30, 2014
- Expiration date: July 30, 2015

To claim CME credit, please read each article and 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. The posttest, evaluation, and CME claim form can be found online at [www.iasusa.org](http://www.iasusa.org).

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 common metabolic complications of HIV infection and long-term antiretroviral therapy and their impact on the management of non-AIDS comorbidities in HIV-infected patients.
- Describe the causes of acute kidney injury and chronic kidney disease in HIV-infected patients on antiretroviral therapy and treatment options for end-stage renal disease in patients with HIV-infection.
- Discuss the increasing number of non-AIDS-defining cancers in the HIV-infected population, factors contributing to these increases, and current screening guidelines to reduce cancer risk.

## Intended Audience

This enduring material is designed for physicians and other health care practitioners who are experienced in the principles of complex chemotherapy (eg, antiretroviral therapy) and are actively treating or will be treating patients with HIV infection.

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

## Disclosure of Financial Interests

In the interest of maintaining the independence of its CME activities, and in accordance with the policies of the Accreditation Council for Continuing Medical Education (ACCME), the IAS–USA requires all persons with control of content (ie, faculty, IAS–USA Board members, and program staff) to disclose any financial relationships that they (or their spouses or partners) have had with commercial companies within the past 12 months. Any real or apparent conflicts of interest of those parties are resolved prior to the continuing medical education activity being delivered. Individuals who refuse to disclose financial interests may not participate in an IAS–USA CME activity.

**Financial Affiliations:** Dr Overton has received research funding through the University of Alabama Birmingham School of Medicine from Gilead Sciences, Inc, AbbVie, Vertex Pharmaceuticals, Inc, and Bristol-Myers Squibb. He has served as a consultant to Gilead Sciences, Inc, and Johnson & Johnson. Dr Wyatt has received grants and research support from Gilead Sciences, Inc, and payment for development of internal educational presentations for Bristol-Myers Squibb employees. Dr Mitsuyasu has received grants or research support from Bionor Immuno, Calimmune, Janssen Therapeutics, and Sangamo Biosciences and travel support from Merck & Co, Inc. He has served as an advisory consultant for Merck & Co, Inc, and EMD Serono and owns stock in Amgen. Dr Richman has been a consultant to Bristol-Myers Squibb, Chimerix, Gen-Probe, Inc, Gilead Sciences, Inc, Sirenas, Prism, and Monogram Biosciences, Inc. He owns stock in Chimerix. Dr Benson has no relevant financial affiliations to disclose. Disclosure information for her spouse, Robert T. Schooley, MD, is indicated below. Dr Hirsch has no relevant financial affiliations to disclose. Ms Jacobsen has no relevant financial affiliations to disclose. Dr Schooley has received research support from Bristol-Myers Squibb and Boehringer Ingelheim Pharmaceuticals, Inc, and has served as a scientific advisor to CytoDyn and Merck & Co, Inc, as a scientific advisory board member for Gilead Sciences, Inc, Globelimmune, Inc, and Monogram Biosciences, Inc, and as a member of data monitoring committees for Axio and Gilead Sciences, Inc. He has stock in Globelimmune, Inc.

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# Fall 2014 Live Continuing Medical Education Courses

IAS–USA CME course announcements are paperless. Please watch for e-mail updates, and visit [www.iasusa.org](http://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™*.

## Improving the Management of HIV Disease®: Full-Day Courses

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.

**New York, New York**  
**Thursday, October 30, 2014**  
 Marriott Marquis

## Hepatitis C Virus Infection: Looking Beyond the Interferon Alfa Era: Full-Day Courses

The **full-day, advanced** CME courses are 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 (HCV)-infected patients, in what has become an exciting new era in HCV care.

**Atlanta, Georgia**  
**Wednesday, October 1, 2014**  
 Georgia Tech Global Learning Center

**Chicago, Illinois**  
**Monday, October 13, 2014**  
 Gleacher Center

## Evolving Strategies in Hepatitis C Virus Management: Small-Group Workshops

Part of the IAS–USA focus on the management of HCV infection, the **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.

**Miami, Florida**  
**Monday, September 22, 2014**  
 JW Marriott Miami

**Boston, Massachusetts**  
**Tuesday, October 14, 2014**  
 Omni Parker House

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**TBD, Fall 2014**

**New Orleans, Louisiana**  
**TBD, Fall 2014**

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**TBD, Fall 2014**

**Seattle, Washington**  
**TBD, Fall 2014**

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**Educational Resources** from past live courses are available on the IAS–USA website at [www.iasusa.org](http://www.iasusa.org), including webcasts (available for CME credit), podcasts, downloadable key slides from lectures, and various presentation handouts.

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For information about any of these programs, please contact the IAS–USA.  
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**Special Contribution****2014 Update of the Drug Resistance Mutations in HIV-1**

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

This July 2014 edition of the IAS–USA drug resistance mutations list updates the figures last published in March 2013.<sup>1</sup>

The following mutations have been added to existing classes or drugs: K65E/N has been added to the bars for the nucleoside and nucleotide analogue reverse transcriptase inhibitors (nRTIs) abacavir, didanosine, emtricitabine, lamivudine, stavudine, and tenofovir<sup>2</sup>; L100I has been added to the bar for the nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) rilpivirine<sup>3,4</sup>; and F121Y has been added to the bars for the integrase strand transfer inhibitors (INSTIs) dolutegravir, elvitegravir, and raltegravir.<sup>5,6</sup> With regard to protease inhibitors (PIs), it cannot be excluded that drug resistance may be selected for outside the protease encoding region.<sup>7,8</sup>

**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 Food and Drug Administration (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 lamivudine or emtricitabine or the 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

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Dr Wensing (Group Chair), University Medical Center Utrecht, The Netherlands; Dr Calvez, Pierre et Marie Curie University and Pitié-Salpêtrière Hospital, Paris, France; Dr Günthard, University Hospital Zurich, University of Zurich, Switzerland; Dr Johnson, Birmingham Veterans Affairs Medical Center and the University of Alabama at Birmingham School of Medicine; Dr Paredes, HIV Unit and IrsiCaixa AIDS Research Institute, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; Dr Pillay, University College London, United Kingdom, and Africa Centre for Health and Population Studies, University of KwaZulu Natal, Mtubatuba, South Africa; Dr Shafer, Stanford University Medical School, Stanford, California; Dr Richman (Group Vice-Chair), Veterans Affairs San Diego Healthcare System and University of California San Diego.

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<sup>9</sup> and 2014 IAS–USA panel recommendations for antiretroviral therapy.<sup>10</sup> Updates are posted periodically at [www.iasusa.org](http://www.iasusa.org).

## Comments

Please send your evidence-based comments, including relevant reference citations, to the **journal** “at” [iasusa.org](http://iasusa.org) or by fax to 415-544-9401.

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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.**

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

**Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)<sup>a</sup>**

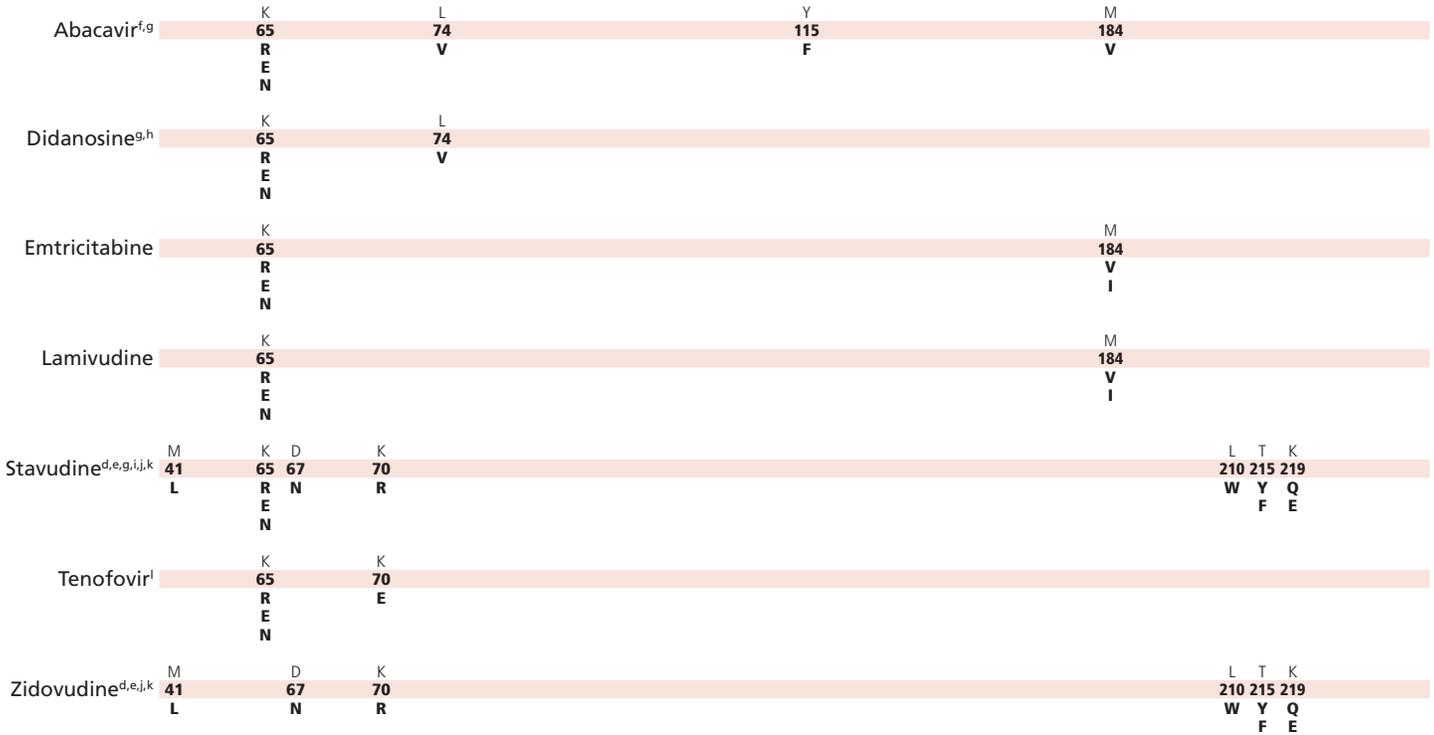
Multi-nRTI Resistance: 69 Insertion Complex<sup>b</sup> (affects all nRTIs currently approved by the US FDA)



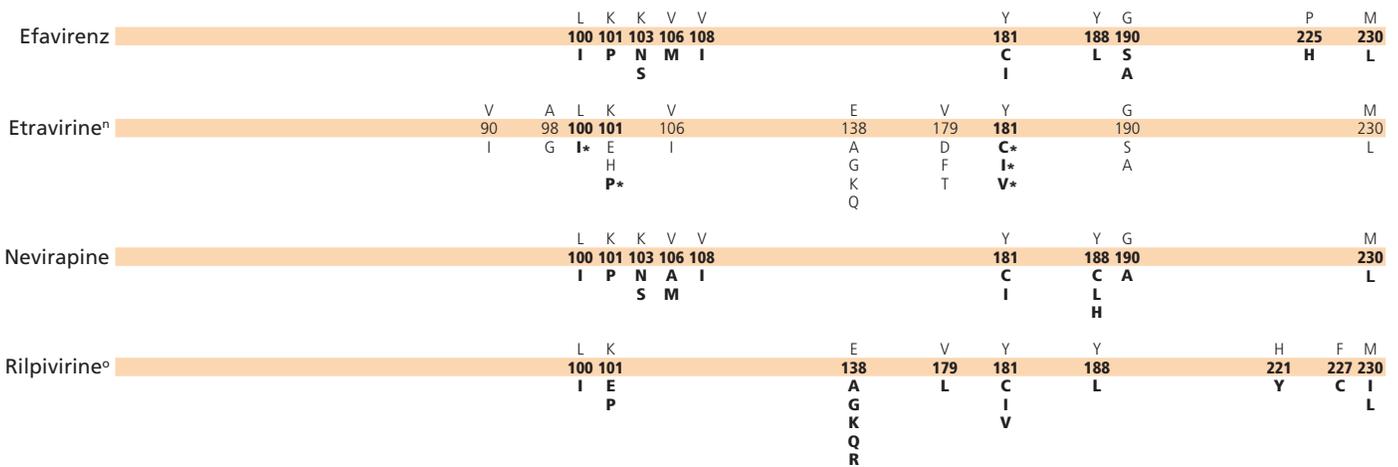
Multi-nRTI Resistance: 151 Complex<sup>c</sup> (affects all nRTIs currently approved by the US FDA except tenofovir)



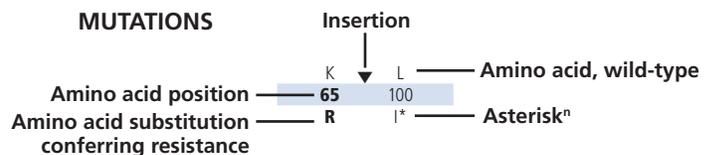
Multi-nRTI Resistance: Thymidine Analogue-Associated Mutations<sup>d,e</sup> (TAMs; affect all nRTIs currently approved by the US FDA)



**Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)<sup>a,m</sup>**



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<sup>p,q,r</sup>**

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

Enfuvirtide <sup>y</sup>	G 36	I 37	V 38	Q 39	Q 40	N 42	N 43
	D	V	A	R	H	T	D
	S		M				
			E				

Maraviroc<sup>z</sup> See User Note

**MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS<sup>aa</sup>**

Dolutegravir <sup>bb</sup>					F 121	E 138	G 140	Q 148
					Y	A	S	H
						K	A	
Elvitegravir <sup>cc</sup>	T 66			E 92	T 97	F 121	S 147	Q 148
	I			Q	A	Y	G	R
	A			G			H	H
	K						K	K
Raltegravir <sup>dd</sup>		L 74	E 92	T 97	F 121	E 138	G 140	Y 143
		M	Q	A	Y	A	A	R
						K	S	H
								C
								R
								R

## User Notes

**a.** Some nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) mutations, like T215Y and H208Y,<sup>1</sup> may lead to viral hypersusceptibility to the nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs), including etravirine,<sup>2</sup> in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens (nevirapine or efavirenz) in NNRTI-naïve individuals,<sup>3-7</sup> 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.<sup>8-10</sup> K65E/N variants are increasingly reported in patients experiencing treatment failure with tenofovir, stavudine, or didanosine. K65E usually occurs in mixtures with wild type. K65N gives an approximately 4-fold decrease in susceptibility. Patient-derived viruses with K65E and site-directed mutations replicate very poorly in vitro; as such, no susceptibility testing can be performed.<sup>11,12</sup>

**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.<sup>13</sup> 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.<sup>15</sup> 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.<sup>14</sup> The degree to which cross-resistance is observed depends on the specific mutations and number of mutations involved.<sup>15-18</sup>

**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.<sup>19-21</sup>

**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.<sup>22,23</sup>

**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.<sup>22,24,25</sup> 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.<sup>26</sup> The presence of K70R or M184V alone does not decrease virologic response to didanosine.<sup>27</sup>

**i.** K65R is selected frequently (4%–11%) in patients with some nonsubtype-B clades for whom stavudine-containing regimens are failing in the absence of tenofovir.<sup>28,29</sup>

**j.** The presence of M184V appears to delay or prevent emergence of TAMs.<sup>30</sup> 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-naïve patients.<sup>31,32</sup> The T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine.<sup>33</sup>

**l.** The presence of K65R is associated with a reduced virologic response to tenofovir.<sup>13</sup> A reduced response also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W.<sup>13</sup> The presence of TAMs or combined treatment with zidovudine prevents the emergence of K65R in the presence of tenofovir.<sup>34-36</sup>

**m.** There is no evidence for the utility of efavirenz, nevirapine, or rilpivirine in patients with NNRTI resistance.<sup>37</sup>

**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.<sup>38-40</sup> Asterisks (\*) are used to emphasize higher relative weights with regard to reduced susceptibility and reduced clinical response compared with other etravirine mutations.<sup>41</sup> The single mutations L1001\*, K101P\*, and

Y181C\*/I\*/V\* reduce clinical utility. The presence of K103N alone does not affect etravirine response.<sup>42</sup> Accumulation of several mutations results in greater reductions in susceptibility and virologic response than do single mutations.<sup>43-45</sup>

**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).<sup>46-48</sup> A 16th mutation, Y188L, reduces rilpivirine susceptibility 6-fold.<sup>49</sup> K101P and Y181I/V reduce rilpivirine susceptibility about 50-fold and 15-fold, respectively, but are uncommonly observed in patients receiving rilpivirine.<sup>50-52</sup> 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 about 7-fold and 4.5-fold, respectively.<sup>52-55</sup> The combinations of reverse transcriptase mutations L1001 + K103N/S and L1001 + K103R + V179D were strongly associated with reduced susceptibility to rilpivirine. However, for isolates harboring the L1001/K103N/R/S or V179D as single mutations, no reduction in susceptibility was detected.<sup>48,56</sup>

**p.** Often, numerous mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI).<sup>57</sup> 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.

Mutations in the cytoplasmic tail of gp41 of *env* or mutations in *gag* cleavage sites may confer resistance to all protease inhibitors and may emerge before mutations in protease do.<sup>58,59</sup> A large proportion of virus samples from patients with confirmed virologic failure on a PI-containing regimen is not found to have PI resistance mutations. Preliminary

data from recent studies suggest that several mutations in the Gag protein<sup>60</sup> and in the cytoplasmic tail of the Env protein<sup>59</sup> may be responsible for reduced PI susceptibility in a subset of these patients.

**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.<sup>61</sup>

**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.<sup>62,63</sup> 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<sup>64</sup> and is associated with a diminished virologic response.<sup>65</sup>

**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.<sup>66,67</sup> The product information states that accumulation of 7 or 8 mutations confers resistance to the drug.<sup>68</sup> However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I, are associated with high-level resistance.<sup>69-71</sup> The addition of L76V to 3 PI resistance-associated mutations substantially increases resistance to lopinavir/ritonavir.<sup>61</sup>

**w.** In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI mutations.<sup>72</sup>

**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.<sup>73-75</sup>

**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.<sup>76-78</sup>

**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 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.<sup>79</sup> The clinical significance of such mutations is not yet known.

**aa.** In site-directed mutants and clinical isolates, the mutation F121Y has a profound effect on susceptibility to elvitegravir and raltegravir and to a lesser extent to dolutegravir.<sup>59,60</sup>

**bb.** Cross-resistance studies with raltegravir- and elvitegravir-resistant viruses 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<sup>80</sup> and reduced virologic suppression in patients.<sup>81-84</sup> Results of the phase III dolutegravir study in antiretroviral treatment-naïve patients are expected to provide additional resistance information.

**cc.** Six elvitegravir codon mutations have been observed in integrase strand transfer inhibitor treatment-naïve and -experienced patients in whom therapy is failing.<sup>85-91</sup> T97A results in only a 2-fold change in elvitegravir susceptibility and may require additional mutations for resistance.<sup>88,89</sup> The sequential use of elvitegravir and raltegravir (in either order) is not recommended because of cross-resistance between these drugs.<sup>88</sup>

**dd.** 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.<sup>92</sup> The Y143R/H/C mutation is uncommon.<sup>93-97</sup> E92Q alone reduces susceptibility to elvitegravir more than 20-fold and causes limited (<5-fold) cross resistance to raltegravir.<sup>87,98-100</sup> 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+Q148H/R/K, with continuing raltegravir treatment.<sup>93</sup>

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## Perspective

# Metabolic Complications of HIV Infection and Its Therapies

*Non-AIDS morbidity and mortality are increasingly common in the HIV-infected population. Chronic inflammation and immunosenescence result in early onset of conditions associated with aging, including atherosclerosis and frailty. Risk for non-AIDS-related morbidity is also related to the metabolic effects of antiretroviral therapy and the increased prevalence of traditional cardiovascular and other risk factors in the HIV-infected population. Risk reduction is centered on maintaining full viral suppression and aggressively implementing measures to reduce standard modifiable risk factors. This article summarizes a presentation by Edgar Turner Overton, MD, at the IAS-USA continuing education program held in New York, New York, in October 2013.*

**Keywords:** cardiovascular disease, chronic inflammation, diabetes, frailty, HIV, immunosenescence, non-AIDS morbidity, obesity

As of 2013, approximately 90% of HIV-infected patients engaged in care in Ryan White HIV/AIDS Program clinics throughout the United States are on fully suppressive antiretroviral therapy, with viral replication being fully suppressed in most individuals. As AIDS-related mortality has decreased, a substantial challenge facing practitioners is the increasing prevalence of non-AIDS morbidity and mortality in HIV-infected patients. Diseases that are increasingly common in the HIV-infected population include diabetes, cardiovascular disease, kidney problems, cognitive impairment, osteoporosis, hypogonadism, and frailty. These conditions, many of which are associated with aging in the general population, appear to occur prematurely or at an accelerated rate in the HIV-infected population. An example of the shift from AIDS-related to non-AIDS-related mortality is provided by a 2006 ART-CC (Antiretroviral Therapy Cohort Collaboration) study showing that the frequency of opportunistic infection as cause of death in HIV-infected patients decreased from 32% in the pre-potent antiretroviral therapy era to 19% thereafter, with the proportion of deaths increasing from 3.2%

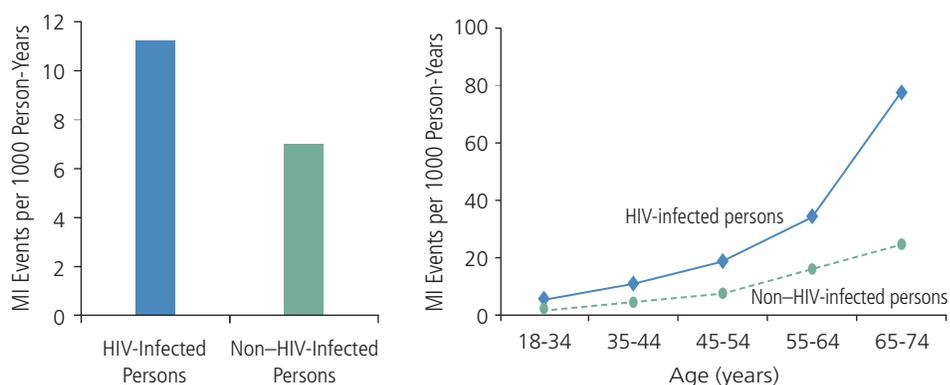
to 9.9% for hepatitis and liver disease, from 2.5% to 4.9% for non-AIDS malignancies, and from 1.3% to 4.3% for cardiovascular disease and diabetes.<sup>1,2</sup>

### Atherosclerotic Heart Disease

Although there has been much debate about cardiovascular risk in HIV infection, the preponderance of data points to a 1.5- to 2-fold higher risk of myocardial infarction (MI) or other cardiovascular death in HIV-infected persons than in HIV-uninfected persons. A study by Triant and colleagues, for example, showed a relative risk for MI of 1.75 in HIV-infected patients, and as shown in Figure 1, the MI event curves for the HIV-infected and HIV-uninfected groups separate at an early

age, with the difference increasing with advancing age.<sup>3</sup> These findings suggest that there is accumulating risk of MI in HIV-infected patients, likely representing a combination of factors that includes prolonged exposure to antiretroviral therapy and presence of other HIV-related comorbidities. The increasing frequency of cardiovascular disease with aging is of particular concern given the estimate that 50% of HIV-infected patients will be older than 50 years by 2015.<sup>4</sup>

Modifiable risk factors for cardiovascular heart disease include inactivity and poor diet, abdominal obesity, smoking, hypertension, hyperglycemia, insulin resistance, and lipid abnormalities. In addition to these risk factors, HIV-infected patients are subject to risk posed by the infection itself and by potential adverse metabolic effects of antiretroviral therapy, both of which can contribute to cardiovascular disease and other non-AIDS-defining comorbidities. HIV infection leads to chronic immune activation and inflammation, alters lipoproteins to produce an atherogenic lipid profile, induces a hypercoagulable state, and results in CD4+ T cell depletion and immunosenescence. Antiretroviral therapy has some toxicity, including insulin resistance, an atherogenic lipid



**Figure 1.** Rates of myocardial infarction (MI; left) and rates of MI by age (right) in HIV-infected and HIV-uninfected persons. Adapted from Triant et al.<sup>3</sup>

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profile, mitochondrial toxicity, and body fat changes. Uncontrolled HIV viremia leads to endothelial dysfunction mediated by immune activation that can be partially offset by antiretroviral therapy.

Thus, the first step in addressing cardiovascular risk in HIV-infected patients is to suppress viral replication with antiretroviral therapy. However, even with suppression of viremia, residual vascular inflammation poses a risk, including an increase in the number of metabolically active macrophages and the frequency of noncalcified, metabolically active, rupture-prone plaques.<sup>5,6</sup> These plaques have been observed in HIV-infected patients at a median age of 40 years to 45 years and differ from the more stable calcified plaques typically seen in aging.

To address modifiable risk factors, practitioners should focus on the ABCD'S of cardiovascular risk management: aspirin, blood pressure, cholesterol, diabetes, and smoking. An example of how efforts to reduce modifiable risk factors may be resulting in disease reduction is provided by recent data from the Kaiser Permanente health care system in California.<sup>7</sup> During the years 2002 through 2003, the crude rate of hospitalization for MI in HIV-infected members reached a high of 3.7 per 1000 person-years, statistically significantly higher than the rate of 1.7 per 1000 person-years in HIV-uninfected members ( $P < .001$ ). Data from 2006 through 2008 indicate that the rate decreased to 2.5 per 1000 person-years in HIV-infected members, which is not statistically significantly different from the rate of 2.0 per 1000 person-years in the HIV-uninfected population ( $P = .088$ ) and marks the first period since before 1996 in which there was no statistically significant difference in the hospitalization rates for MI among the 2 groups. Over the same period of 1996 through 2008, the use of lipid-lowering therapy in HIV-infected members on antiretroviral therapy increased from virtually 0% (in 1996 and 1997) to greater than 30% in patients on combination antiretroviral regimens.

## Frailty

Frailty is characterized by unintentional weight loss, weakness (typically manifested as reduced grip strength or proximal muscle weakness), symptoms of exhaustion, slowness (measured as slowing on a timed walk), and decreased physical activity. A diagnosis of frailty is commonly based on the presence of at least 3 of these 5 associated characteristics.<sup>8</sup> Frailty typically occurs as part of the aging process late in the lifetime of a person or animal. It is considered an end-stage process and consists of loss of functional homeostasis (eg, immune and endocrine dysregulation), leaving individuals unable to recover fully after stressors and predisposing them to poor health outcomes, including increased morbidity and mortality.

In conditions of heightened inflammation, such as rheumatoid arthritis and HIV infection, what appears to be accelerated aging occurs, with those affected becoming frail at earlier ages than those without such conditions. For example, a 2011 MACS (Multicenter AIDS Cohort Study) report demonstrated that frailty (defined as the presence of at least 3 of the 5 above conditions) was present in 14.8% of HIV-infected men versus 8.1% of matched HIV-uninfected controls aged 50 years to 59 years, 19.9% versus 10.0% of those aged 60 years to 69 years, and 33% versus 23% of those older than 69 years.<sup>9</sup>

With regard to similarities and differences in frailty characteristics among the elderly and HIV-infected patients, prevalence in the elderly increases from approximately 3% to 5% at age 65 years to 32% at age 90 years, whereas prevalence in HIV-infected groups has been reported at 5% to 20% at median ages of between 40 years and 50 years. In the elderly, prevalence is greater among women than men and greater among Hispanics and US blacks than among US whites, with the lowest prevalence found among European whites. In contrast, there do not appear to be differences in prevalence by race or sex among HIV-infected persons.<sup>10-15</sup> In the frail elderly, there is increased comorbidity, including cognitive impairment and

depression, postoperative risk, falls, cross-infection, polypharmacy, social isolation, hospitalization, institutionalization, and high mortality risk. There is similar increased morbidity, including cognitive impairment and depression, in HIV-associated frailty, as well as increased nonelective hospitalization, duration of inpatient stay, and unemployment.<sup>10,14</sup>

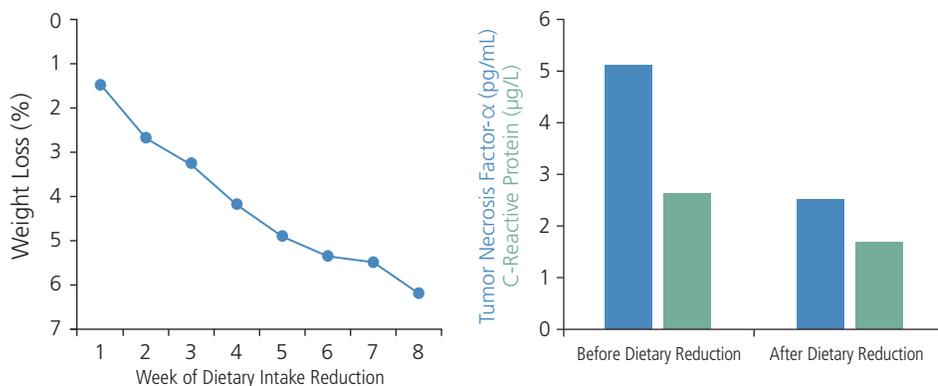
Inflammation and immunosenescence have been associated with frailty in the geriatric and HIV-infected populations. In the elderly, residual, or sterile, inflammation occurs when inflammatory response results in terminally differentiated T cells with a senescent profile. Accumulation of these T cells results in a proinflammatory milieu that is nonresponsive to new antigen challenges. In the elderly, this process has been associated with chronic viral infection, most notably cytomegalovirus infection. What may be occurring in the HIV-infected population is chronic inflammation and an acceleration of immunosenescence that result in a frailty phenotype.

## Obesity and Inflammation

Obesity also contributes to systemic inflammation. As people become obese, fat cells in abdominal and visceral fat increase in size and begin to secrete cytokines that recruit macrophages and activated T cells into the adipose tissue. Inflammation results from the accumulation of these cells and the induction of apoptosis of the fat cells by activated T cells. The fat cells then release proinflammatory cytokines and oxidized lipoproteins that contribute to chronic inflammation.

## Reducing Inflammation

Interventions to reduce inflammation that are of particular importance in HIV-infected patients are to maintain maximum viral suppression with antiretroviral therapy, stop smoking, maintain normal weight or lose at least 5% to 10% of body weight if overweight, exercise, consume a healthy diet, reduce alcohol intake, and avoid illicit drug use.



**Figure 2.** Effect on weight (left) and inflammatory markers (right) of reducing dietary intake by 500 calories per day for 8 weeks in obese persons. Adapted from Hermsdorff et al.<sup>15</sup>

Figure 2 shows the marked effect that a reduction in dietary intake of 500 calories per day can have on body weight and markers of inflammation in obese persons. After 8 weeks, participants lost 6% of body weight and showed a marked decline in levels of the markers of systemic inflammation tumor necrosis factor-α and C-reactive protein.<sup>15</sup>

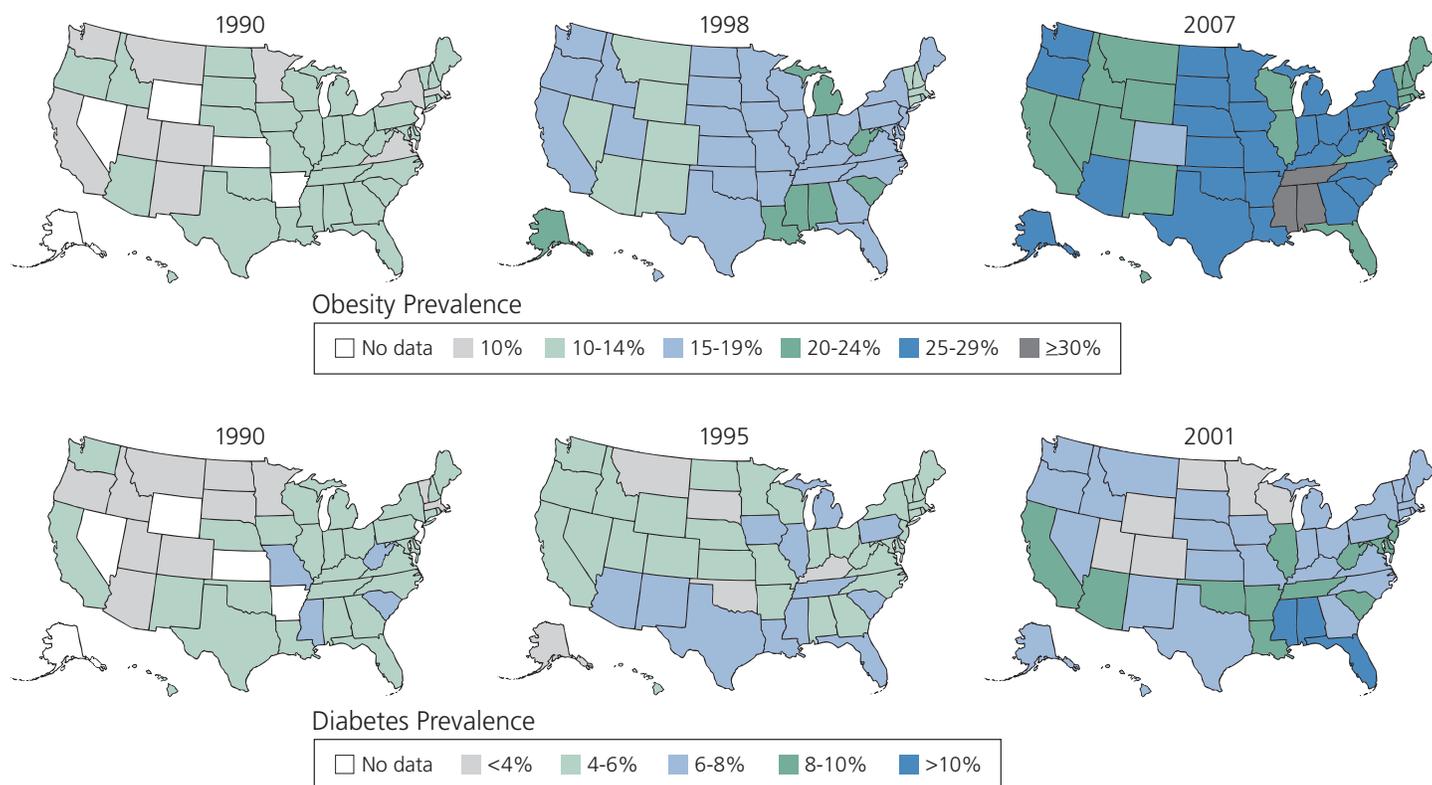
Calorie-dense foods and portion distortion are now major problems in America. Rather than eating a 600-calorie, quarter-pound hamburger, many Americans eat a 1300-calorie, half-pound hamburger with supersized fries. Twenty years ago, a plain bagel was 3 inches in diameter and contained 140 calories, but today's bagel is 6 inches across and contains 350

calories. Figure 3 shows the increasing prevalence of obesity and diabetes in the United States over the past 10 years to 20 years.<sup>16-18</sup>

Obesity is increasingly common in HIV-infected patients. Recently reported data from the SUN (Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy) study, which included a representative sample of 494 patients (78% male, 61% white, 27% black, and 10% Hispanic) with a median body mass index of 26 kg/m<sup>2</sup>, showed that approximately 23% of patients were obese, 38% were overweight, 38% were normal weight, and 2% were underweight. Obesity was associated with insulin resistance, elevated levels of cholesterol and inflammatory markers, and increased atherosclerosis.<sup>19</sup>

### Conclusions

The increasing prevalence of non-AIDS comorbidities in HIV-infected



**Figure 3.** Increasing prevalence of obesity (BMI ≥ 30) from 1990 to 2007 (top) and of diabetes (including gestational diabetes) from 1990 to 2001 (bottom) in the United States. Adapted from Centers for Disease Control and Prevention<sup>16</sup> and Mokdad et al.<sup>17,18</sup>

patients reflects a number of factors. Traditional risk factors play a contributing role and include genetics, diet, environmental factors, and lifestyle determinants such as tobacco, alcohol, or illicit drug use. HIV infection itself increases the risk of developing comorbidities through persistent inflammation and immune activation, and long-term antiretroviral therapy adds to this risk through direct toxic effects, insulin resistance, promotion of an atherogenic lipid profile, mitochondrial toxicity, and associated body fat changes.

Goals for the future include more clearly identifying the respective roles of HIV infection and antiretroviral therapy in the risk for developing comorbidities and determining whether these effects are reversible, including whether early institution of antiretroviral therapy is important in this regard. Although some aspects of the management of metabolic and inflammatory dysregulation in HIV-infected patients may differ from the management of risk factors in HIV-uninfected persons, a major component of risk reduction remains a heavy emphasis on reducing standard, modifiable risk factors. 

*Presented by Dr Overton in October 2013. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Overton in May 2014.*

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*Inc, and Bristol-Myers Squibb. He has served as a consultant to Gilead Sciences, Inc, and Johnson & Johnson.*

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## Perspective

# Antiretroviral Therapy and the Kidney

*Acute kidney injury (AKI) and chronic kidney disease (CKD) are more common in the HIV-infected population than in the general population. AKI is associated with an increased risk of heart failure, cardiovascular disease, end-stage renal disease (ESRD), and mortality. Tenofovir is associated with severe AKI in a small percentage of patients and with subclinical abnormalities in many more. HIV-associated nephropathy is now a relatively rare form of CKD, because of the widespread use of potent antiretroviral therapy. The CKD spectrum in HIV-infected patients has become more frequently characterized by comorbid CKD, with an increased frequency of CKD related to diabetes or hypertension being observed. Kidney transplantation is a therapeutic option for HIV-infected patients with ESRD if their HIV infection is controlled, although rates of acute graft rejection and drug-drug interactions are high. This article summarizes a presentation by Christina M. Wyatt, MD, at the IAS–USA continuing education program held in Washington, DC, in June 2013.*

**Keywords:** acute kidney injury, chronic kidney disease, end-stage renal disease, HIV, nephrotoxicity, renal, tenofovir, toxicity, transplantation

## Acute Kidney Injury

Acute kidney injury (AKI) is more common in HIV-infected patients than in the general population and is associated with poorer health outcomes in those with HIV infection, including increased rates of heart failure, cardiovascular disease, end-stage renal disease (ESRD), and mortality. Even stage I AKI is associated with an increased risk of ESRD and mortality (Figure 1).<sup>1,2</sup>

In a 2005 study of more than 700 HIV-infected patients, approximately 10% of patients experienced at least 1 episode of AKI over the 2-year follow-up period. The investigators determined that 52% of cases were caused by systemic infections, 76% of which were AIDS-defining infections.<sup>3</sup> Thirty-two percent of cases were caused by drug toxicity, with most cases attributed to the use of  $\beta$ -lactam or aminoglycoside antibiotics and some to the antiretroviral drugs indinavir and tenofovir, radiocontrast agents, nonsteroidal antiinflammatory drugs, or lithium. Another 10% of cases were attributed to liver failure, with 90% of these occurring in patients with hepatitis C virus (HCV) coinfection.

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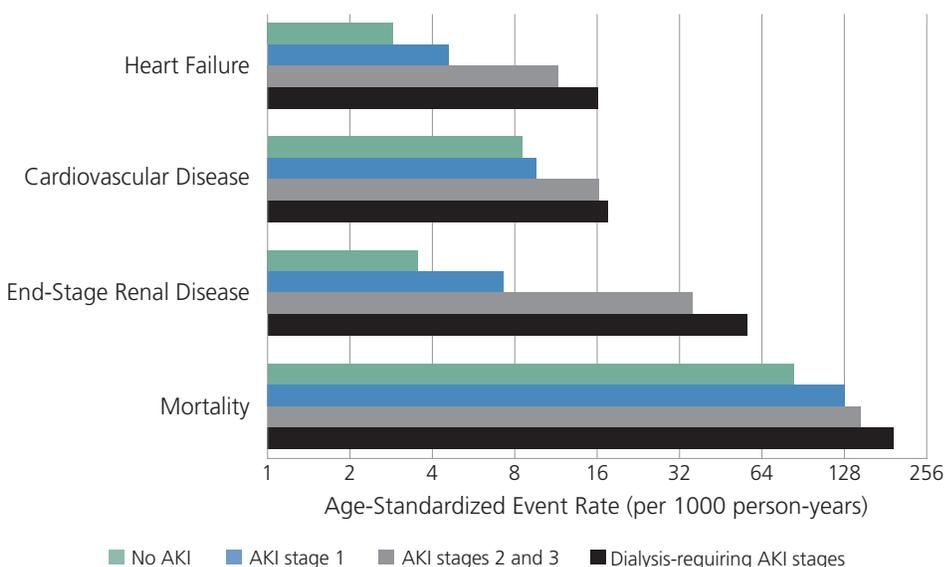
## Case Study

A 56-year-old, HIV/HCV-coinfected, African American woman with well-compensated cirrhosis presented to her primary care practitioner in the HIV clinic with a complaint of vomiting that persisted for 2 weeks. Her most recent CD4+ cell count was approximately 300/ $\mu$ L and her nadir CD4+ cell count was less than 100/ $\mu$ L. Her antiretroviral

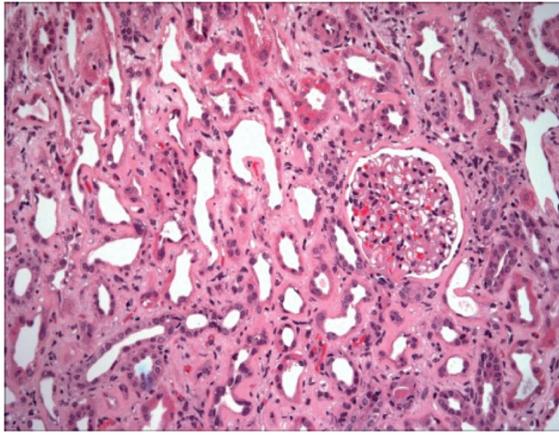
regimen consisted of tenofovir, emtricitabine, and ritonavir-boosted (*/r*) lopinavir. She had also been taking ibuprofen for malaise.

Her laboratory results were remarkable for a serum creatinine level of 21 mg/dL (the most recent serum creatinine was 1.4 mg/dL), a blood urea nitrogen level of 78 mg/dL, a serum potassium level of 3.9 mEq/L, and a serum bicarbonate level of 15.2 mEq/L. Urinalysis showed protein, ketones, and glucose (serum glucose was normal), and a normal bowel gas pattern was found on plain film radiographic examination. Additional laboratory evaluation showed a serum phosphorus level of 5.2 mg/dL and a urine sodium level of 60 mEq/L.

The most likely cause of AKI in this case is tenofovir toxicity. Although the classic presentation of tenofovir toxicity is proximal tubulopathy, the classic electrolyte deficiencies (hypophosphatemia, hypokalemia, hypouricemia) may not be present in patients who present with severely reduced glomerular filtration rate; in this case, the absence of hyperkalemia in the context of renal failure and acidosis was notable. The finding of urine glucose in the setting of a normal



**Figure 1.** Acute kidney injury (AKI), by stage, and its association with risk for heart failure, cardiovascular events, end-stage renal disease, and mortality, beginning 90 days after discharge from in-hospital AKI treatment. Adapted from Choi et al.<sup>2</sup>



**Figure 2.** Kidney biopsy showing the effects of tenofovir renal toxicity. Courtesy of Glen S. Markowitz, MD, and Vivette D. D'Agati, MD.

serum glucose (euglycemic glycosuria) is another indicator of proximal tubular injury. Although the history could suggest hepatorenal syndrome or prerenal AKI, the patient has well-compensated cirrhosis and the high urine sodium level is more consistent with intrinsic kidney damage.

### Tenofovir Toxicity

Although tenofovir was not associated with a statistically significant increase in kidney toxicity in premarketing clinical trials, graded elevations in serum creatinine were observed in 2.2% of patients receiving tenofovir through the manufacturer's expanded access program.<sup>4</sup> Subclinical abnormalities suggesting proximal tubular dysfunction have been observed in 25% to 80% of patients.<sup>5-7</sup> A 2010 meta-analysis of 5 randomized controlled trials of tenofovir and 8 cohort studies of antiretroviral therapy-naïve and -experienced patients showed small but statistically significantly greater reductions in calculated creatinine clearance among tenofovir recipients in the randomized trials, the cohort studies, and all studies combined. Overall, the mean difference between tenofovir recipients and nonrecipients was -3.9 mL/min, with larger differences observed in the cohort studies. A statistically significant decline in tenofovir recipients was observed in only 1 of the controlled trials when analyzed separately.<sup>8</sup>

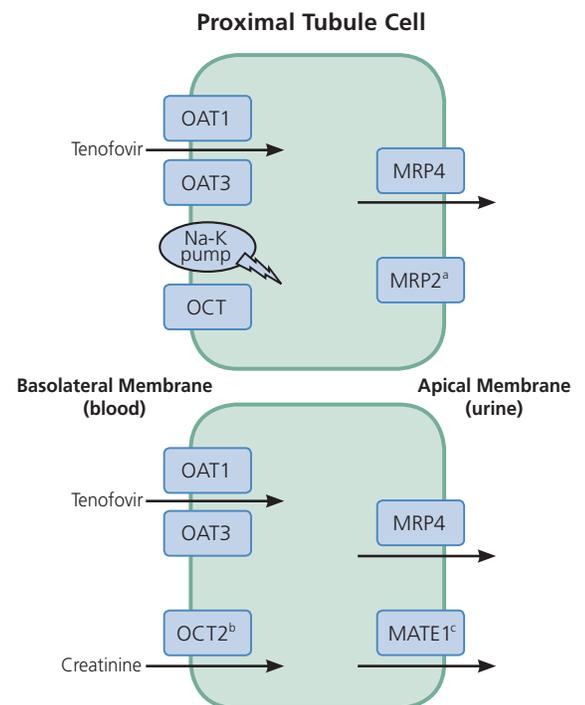
Biopsy is usually not necessary to diagnose tenofovir kidney toxicity. The presentation is generally that of proximal tubulopathy with wasting of phosphorus, glucose, amino acids, and bicarbonate, which are reabsorbed by the proximal tubule under normal circumstances. In most instances, toxicity resolves when tenofovir is discontinued. Biopsy may be warranted when there is a compelling reason not to discontinue tenofovir (eg, in patients with hepatitis B virus coinfection who are not candidates for entecavir or those with an antiretroviral

resistance profile that limits therapeutic options) or if the clinical picture does not clearly suggest tenofovir toxicity. In cases of tenofovir toxicity, biopsy shows damage to the proximal tubule, whereas the glomerulus typically remains unaffected (Figure 2). The advanced fibrosis evident in the figure indicates chronic toxicity. If tenofovir toxicity is identified early, it may be completely reversible, but irreversible damage is likely with chronic toxicity.

More remains to be learned about risk factors for tenofovir toxicity, but unrecognized low glomerular filtration rate (GFR) is an established risk factor, as is concomitant administration of another nephrotoxic drug. Some data suggest a genetic predisposition to tenofovir toxicity, although most of the early studies in this area focused on membrane transport proteins that are not actively involved in tenofovir transport. The transport of tenofovir from the basolateral (blood) side of tubule cells is mediated primarily by organic anion transporter (OAT) 1 and to a lesser extent by OAT3 (Figure 3, top).<sup>9</sup> The exit of tenofovir to the apical (urine) side of tubule cells is mediated by multidrug resistance protein (MRP) 4. Most early genetic studies of tenofovir

toxicity focused on MRP2, based on observation of an association between ritonavir-boosted protease inhibitor (PI) use and tenofovir toxicity, and the known effect of ritonavir in interfering with MRP2-mediated efflux of other drugs. However, more recent studies suggest that the association of boosted PI use with tenofovir toxicity reflects the effect of some boosted PIs in increasing biologic availability and trough blood levels of tenofovir.<sup>10</sup>

Data from the EuroSIDA cohort showed that use versus nonuse of tenofovir, indinavir, atazanavir, or lopinavir/r was associated with a statistically significantly increased risk of developing chronic kidney disease (CKD), manifested as a confirmed creatinine clearance of less than 60 mL/min per 1.73 m<sup>2</sup>.<sup>11</sup> There is evidence indicating that atazanavir, like indinavir but to a lesser degree, can precipitate into crystals, resulting in an inflammatory reaction and interstitial nephritis, a mechanism supported by



**Figure 3.** Tubular transport of tenofovir (top) and effect of antiretroviral therapy on creatinine secretion (bottom). MRP indicates multidrug resistance protein; Na-K, sodium-potassium; OAT, organic anion transporter; OCT, organic cation transporter. Adapted from Ray et al.<sup>9</sup> <sup>a</sup>Inhibited by ritonavir. <sup>b</sup>Inhibited by dolutegravir. <sup>c</sup>Inhibited by trimethoprim, cobicistat, or rilpivirine.

the relatively high levels of atazanavir found in the urine. A similar mechanism may account for the apparent increase in CKD associated with the use of lopinavir/r. Assessment of the relationship between antiretroviral therapy exposure and CKD in the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) cohort showed that on multivariate analysis, tenofovir (incidence rate ratio [IRR], 1.18), lopinavir/r (IRR, 1.11), and atazanavir/r (IRR, 1.19)—but not unboosted atazanavir, other ritonavir-boosted PIs, or abacavir—were associated with a statistically significantly increased risk of having an estimated GFR (eGFR) less than or equal to 70 mL/min per 1.73 m<sup>2</sup>. Only lopinavir/r (IRR 1.22) was associated with a statistically significantly increased risk of having an eGFR less than or equal to 60 mL/min per 1.73 m<sup>2</sup>.<sup>12</sup> The investigators noted a high rate of tenofovir discontinuation at eGFR less than 70 and hypothesized that this may have prevented further declines in kidney function.

Tenofovir was recently approved by the US Food and Drug Administration (FDA) for use in combination with emtricitabine for HIV preexposure prophylaxis (PrEP). Although randomized controlled trials of tenofovir in this setting have not shown overt bone or renal toxicity, it should be remembered that trials of tenofovir in HIV-infected patients also did not show overt bone or renal toxicity, and that most PrEP studies have shown low medication adherence rates. In the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study, a greater decline in creatinine clearance was observed in patients receiving tenofovir in combination with emtricitabine, indicating that renal toxicity may also occur in HIV-uninfected persons receiving tenofovir for PrEP.

Another recent development is the FDA approval of a fixed-dose combination of tenofovir, emtricitabine, elvitegravir, and cobicistat. Cobicistat has been associated with rapid and reversible declines in eGFR with no decrease in measured GFR. This reflects an increase in serum creatinine resulting from decreased tubular creatinine secretion via the multidrug and toxin extrusion protein 1 (MATE1) transporter (Figure 3,

bottom).<sup>9,13</sup> The effect of cobicistat on the MATE1 transporter is similar to but of lesser magnitude than the inhibitory effect of the antibiotic trimethoprim. Studies in vitro have shown that the MATE1 transporter is also inhibited by rilpivirine, another antiretroviral drug used in fixed-dose combination with tenofovir. Dolutegravir may cause an increase in serum creatinine levels similar to that seen with cobicistat use by inhibiting the organic cation transporter 2 (OCT2), which transports creatinine into tubular cells. The average increase in serum creatinine level seen with cobicistat is approximately 0.1 mg/dL to 0.15 mg/dL, although some patients exhibit more marked increases. Increases in serum creatinine levels generally occur very rapidly after initiation of therapy with cobicistat and should be detectable within approximately 2 weeks.

Tenofovir alafenamide fumurate (formerly GS-7430), which is in phase III studies, produces lower plasma levels of tenofovir. Phase II studies of this drug showed reduced adverse effects in bone and kidneys, and pharmacokinetic evaluation indicates that no dose reduction is required in patients with GFRs as low as 15 mL/min per 1.73 m<sup>2</sup> to 30 mL/min per 1.73 m<sup>2</sup>.

## Chronic Kidney Disease

### HIV-Associated Nephropathy

HIV-associated nephropathy (HIVAN)—the classic kidney disease of HIV infection—is decreasing in incidence in the era of aggressive antiretroviral therapy. HIVAN is associated with advanced HIV disease and almost exclusively affects patients of African American or West African descent, as a result of a genetic predisposition that has been well described in the last several years.<sup>14,15</sup>

IAS–USA, Infectious Diseases Society of America, and US Department of Health and Human Services guidelines all indicate that diagnosis of HIVAN is an indication for the initiation of antiretroviral therapy regardless of CD4+ cell count.<sup>16–18</sup> In practice, the guideline to start treatment on the basis of HIVAN rarely needs to be invoked, because most patients have low CD4+

cell counts at the time of presentation with HIVAN and antiretroviral therapy is indicated regardless of CD4+ cell count.

### The Changing Spectrum of CKD

The spectrum of CKD in HIV now reflects an increased frequency of comorbid kidney disease, including increased frequency of diabetes and hypertension, which are the leading causes of ESRD in the general population. Treatment of comorbid disease in HIV-infected patients involves the same measures used in the general population, including tight control of blood pressure and glycemia.

CKD is associated with increased cardiovascular risk, but there are limited data on the effect of risk modification in reducing the incidence of cardiovascular disease in this setting. Drug choice and dosing should be reviewed in patients with comorbid CKD. Kidney biopsy is underused for diagnosis of CKD in the HIV-infected population, particularly in patients who are candidates for kidney transplant. It is helpful to have biopsy information in advance and available data indicate that there is no increase in biopsy procedural risk in HIV-infected patients.<sup>19</sup> Referral to a nephrology specialist for ESRD treatment planning should be made by the time a patient reaches CKD stage 4 (eGFR < 30 mL/min per 1.73 m<sup>2</sup>), if not sooner.

In ESRD treatment, survival outcomes with peritoneal dialysis and hemodialysis are basically equivalent in the HIV-infected population, although infectious complications differ with the 2 modalities.<sup>20</sup> Kidney transplantation is an additional treatment option for ESRD. The best data supporting transplantation in the HIV-infected population come from a large prospective observational study of 150 HIV-infected patients, reported by Stock and colleagues in 2010.<sup>21</sup> To take part in the study, patients had to have undetectable HIV RNA levels and CD4+ cell counts greater than 200/μL and be on a stable potent antiretroviral regimen. Acceptable graft and patient survival rates were achieved and were similar to rates observed in transplant recipients older than 65 years of age in the HIV-uninfected population. There was no apparent increase

in opportunistic infections among study patients; 5 AIDS-defining illnesses, 7 non–AIDS-defining cancers, and 2 cases of biopsy-proven HIVAN were reported; except for the HIVAN cases, these were all conditions known to occur in HIV-uninfected transplant recipients. A high rate of acute graft rejection and marked drug-drug interactions were observed.

PIs can dramatically increase levels of calcineurin inhibitors, such that administration of calcineurin inhibitors may need to be reduced from twice daily to as infrequently as once weekly during concurrent PI use. Although high calcineurin inhibitor levels can be maintained in this manner, there is suspicion that a reduced consistency in exposure may be contributing to the increased rate of acute graft rejection seen in HIV-infected patients. Nonnucleoside reverse transcriptase inhibitors have a more moderate effect in reducing levels of calcineurin inhibitors. Switching patients to PI-sparing regimens prior to kidney transplantation is required by some transplant centers; switching to a PI-sparing regimen after transplantation is also an option, and there are pros and cons associated with both approaches. Limited data are available on the use of tenofovir in HIV-infected transplant recipients, although it appears to be well tolerated.

## Conclusion

AKI and CKD are more common among HIV-infected patients than in the general population. It may be difficult to distinguish antiretroviral nephrotoxicity from other causes of AKI or CKD, and there is an increasing prevalence of comorbid CKD in the HIV-infected population. Patients with controlled HIV infection may be candidates for kidney transplantation, although the potential for severe drug-drug interactions should be recognized. 

Presented by Dr Wyatt in June 2013. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Wyatt in June 2014.

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support from Gilead Sciences, Inc, and payment for development of internal educational presentations for Bristol-Myers Squibb employees.

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## Cases on the Web



### **NEW!** Prevention of Cardiovascular Disease in the HIV-Infected Individual

Michelle Zikusoka, MD, MHS, Wendy S. Post, MD, MS, and Todd T. Brown, MD, PhD

CME Credit Available: **1.50 AMA PRA Category 1 Credits™**

Level: **Advanced**

Given the prevalence of traditional risk factors, the aging of HIV-infected individuals, and the potential cardiovascular consequences of HIV disease and antiretroviral therapy, more attention should be focused on efforts to decrease the morbidity and mortality associated with atherosclerotic cardiovascular disease (ASCVD) and HIV infection. The key to success in CVD prevention is education of the clinician and the patient.

### **NEW!** Geriatrics and HIV

Harjot K. Singh, MD, ScM, and Eugenia Siegler, MD

CME Credit Available: **1.50 AMA PRA Category 1 Credits™**

Level: **Advanced**

The percentage of HIV-infected patients older than 50 years is expected to increase to more than 50% by 2020, based on modeling. Treatment with single-tablet regimens can lead to durable viral suppression. However, viral suppression comes at the price of lifelong treatment and is further complicated by the expected challenges associated with aging itself.

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John J. Faragon, PharmD, BCPS

### **Acute HIV Infection in Men Who Have Sex With Men**

Leah Burke, MD, and Kristen Marks, MD, MS

## SELECTED CURRENT CASES ON THE WEB

### **Hepatitis C Viral Targets**

Stuart C. Ray, MD, Justin R. Bailey, MD, PhD

CME Credit Available: **1.50 AMA PRA Category 1 Credits™**

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A 2008 study by Limketkai and colleagues showed that in patients with HIV/HCV coinfection, hepatic fibrosis stage was independently

associated with risk of progression to end-stage liver disease, hepatocellular carcinoma, and death, and that sustained virologic response after treatment of HCV infection was associated with survival. These findings highlight the importance of staging of liver disease and, whenever possible, treating HCV in HIV/HCV-coinfected individuals.

### **Initiating Antiretroviral Therapy in Resource-Limited Settings**

Habib Ramadhani Omari, MD, MPH, MHS, and John A. Bartlett, MD

CME Credit Available: **1.50 AMA PRA Category 1 Credits™**

Level: **Advanced**

Antiretroviral therapy has been tremendously successful in reducing morbidity and mortality among HIV-infected persons, and an estimated 10,000,000 people globally are now receiving it. Stigma and the need for strict medication adherence are commonly encountered throughout the world. In resource-limited contexts, there is an additional challenge of maintaining a continuous drug supply and having the ability to properly monitor treatment. Early treatment initiation is essential to preserve immunity, prevent the emergence of AIDS-defining illnesses, and decrease HIV transmission.

### **Antiretroviral Drugs as Prevention in Men Who Have Sex With Men: Breakthroughs and Challenges**

Demetre C. Daskalakis, MD

CME Credit Available: **1.50 AMA PRA Category 1 Credits™**

Level: **Advanced**

Several biologic strategies have been added to the HIV prevention toolbox in the past few years to supplement behavioral and barrier methods of prevention. Data from clinical trials support the use of antiretroviral therapy at all phases of transmission and acquisition risk. These treatments, taken daily, may be used before an HIV exposure to prevent transmission. This intervention, called preexposure prophylaxis (PrEP), is used in individuals at high risk for HIV acquisition. Postexposure prophylaxis (PEP), although supported only by limited data in observational studies, may be used immediately after a high-risk exposure to prevent HIV infection. Treatment of people with HIV infection is itself a preventive intervention, with strong evidence of reduction of transmission in serodiscordant partners in some populations.

### **Pregnancy Planning and Preconception Health Care for HIV-Infected Individuals and Couples**

Erika Z. Aaron, MSN, CRNP

CME Credit Available: **1.00 AMA PRA Category 1 Credit™**

Level: **Advanced**

For HIV-serodifferent couples (in which 1 partner is HIV seropositive and the other is HIV seronegative) who desire pregnancy, the goal of safe conception (ie, preventing HIV infection of the fetus and the HIV-seronegative partner) is not easy to realize, because condom use is necessary to minimize the risk of HIV transmission during vaginal intercourse. However, guidelines from the American Society for Reproductive Medicine concerning assisted reproduction for HIV-infected people endorse the use of assisted reproduction techniques in serodifferent couples. HIV health care practitioners should consistently assess for pregnancy desire and offer preconception care to all women with HIV infection who are of childbearing age and to their partners.

### **Selected Endocrine Problems in HIV-Infected Patients**

Todd T. Brown, MD, PhD

CME Credit Available: **1.00 AMA PRA Category 1 Credit™**

Level: **Advanced**

Effective antiretroviral treatments have dramatically reduced morbidity and mortality among HIV-infected patients, and HIV health care professionals are increasingly managing chronic complications of therapy and conditions related to aging. This *Cases on the Web* activity focuses on 2 endocrine abnormalities, diabetes mellitus and adrenal insufficiency, summarizes the current evidence about the optimal evaluation of these disorders, and highlights their causes, presentation, and treatment in HIV-infected patients.

For information about *Cases on the Web*, please contact the IAS–USA.

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## Perspective

# Non–AIDS-Defining Cancers

*As HIV-infected patients are living longer, non–AIDS-defining cancers are increasing in number and now constitute the majority of cancers diagnosed in the HIV-infected population. The excess incidence of Hodgkin lymphoma and head and neck and liver cancers has been increasing among HIV-infected individuals. Breast and lung cancers appear to occur earlier in the HIV-infected population; Hodgkin lymphoma appears to have a later onset, reflecting the fact that most cases in the HIV-infected population are related to Epstein-Barr virus infection, which is generally seen in older rather than younger individuals. Mortality from Hodgkin lymphoma and lung and prostate cancers is higher among HIV-infected individuals than HIV-uninfected individuals. The greater risk of cancer in the HIV-infected population may be due to a number of factors, including more rapid immunosenescence. At a minimum, age- and sex-appropriate cancer screenings should be performed in all HIV-infected patients, and patients should be counseled on measures to reduce cancer risk. This article summarizes a presentation by Ronald T. Mitsuyasu, MD, at the IAS–USA continuing education program held in San Francisco, California, in March 2013.*

**Keywords:** anogenital cancers, cancer incidence, cancer mortality, cancer screening, HIV, Hodgkin lymphoma, immunosenescence, lung cancer, NADCs

HIV-infected individuals are living longer as a result of more effective and better tolerated antiretroviral treatment and fewer risks of opportunistic diseases. The overall incidence of AIDS-defining cancers (ADCs) among HIV-infected individuals has decreased, reflecting lower rates of such cancers as Kaposi sarcoma and non-Hodgkin lymphoma (NHL) in patients aged 40 years or younger. Concurrently, the number of non–AIDS-defining cancers (NADCs) among HIV-infected individuals has increased owing in large part to diagnoses in patients older than 40 years of age. Thus, the number of NADCs diagnosed each year in the HIV-infected population has now surpassed the number of ADCs.<sup>1</sup>

### Increase in Non–AIDS-Defining Cancers

Data from HIV and cancer matched registries in the United States have shown

that among the HIV-infected population, NADCs accounted for 31.4% of all cancers reported from 1991 to 1995 and that this proportion increased to 58% from 1996 to 2002.<sup>2</sup> Standardized incidence ratios were used to compare NADC incidence in the HIV-infected population with that in the general population, with data indicating an increase in the standardized incidence ratio for some NADCs and stable values for others from the earlier to the later period. Standardized incidence ratios increased for laryngeal cancer (from 1.8 to 2.7), liver cancer (from 0 to 3.7), and Hodgkin lymphoma (from 2.8 to 6.7) but remained stable for lung cancer (from 2.6 to 2.6) and anal cancer (from 10.0 to 9.1).<sup>1</sup>

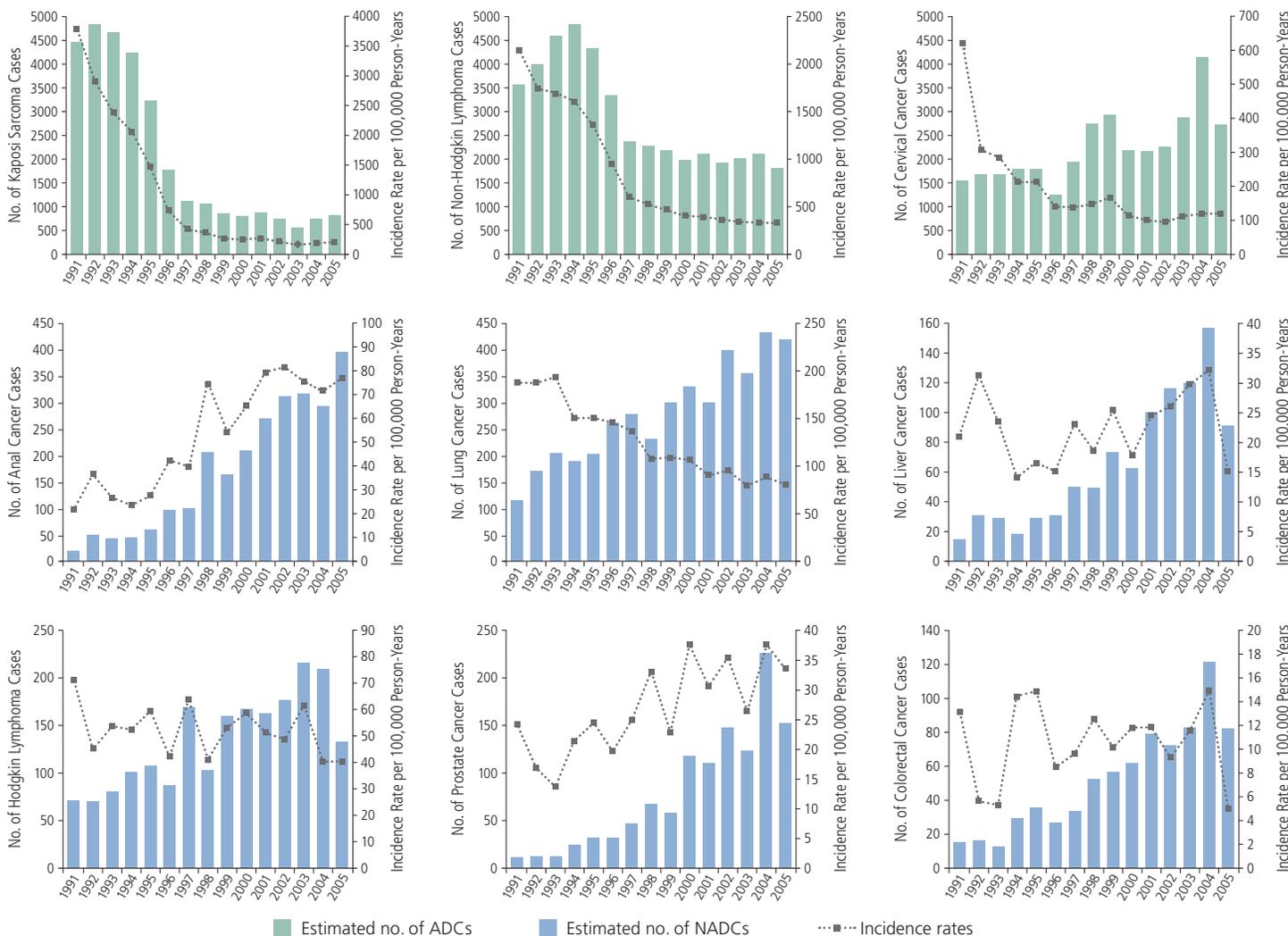
As shown in Figure 1, in the United States between 1991 and 2005, Kaposi sarcoma and NHL cases decreased in number and incidence in the HIV-infected population; anal and prostate cancers increased in number and incidence; cervical, liver, and colorectal cancers and Hodgkin lymphoma cases increased in number but maintained a relatively stable incidence; and lung cancers increased in number but decreased

somewhat in incidence.<sup>1</sup> Factors contributing to the increase in cancer cases among HIV-infected individuals include the approximately 4-fold increase in the size of the HIV-infected population over this time period, higher smoking rates and earlier smoking initiation among HIV-infected individuals, increasing number of HIV-infected patients who are 50 years of age or older, increased incidence of cancer with advancing age, and higher risk of developing cancers among immunodeficient individuals.

Epidemiologic data raise the important question of whether HIV infection itself may be associated with an increased risk of developing cancer at an earlier age than in the general population. A study by the National Cancer Institute (NCI) using data from HIV and cancer matched registries indicates that this is the case for some cancers but not others.<sup>3</sup> Figure 2 shows the observed number and age distribution of cancer cases in the HIV-infected and general populations in the United States between 1996 and 2007 and the expected cancer rate in the general population when modeled to have the same age distribution as the HIV-infected population.<sup>3</sup>

The curve for the HIV-infected population is left-shifted compared with the curve for the expected rate in the age-adjusted general population for some of these cancers, such as for liver and lung cancers. The curve for Hodgkin lymphoma in HIV-infected individuals, however, is right-shifted, indicating that this cancer develops more commonly at later ages in the HIV-infected population than in the general population. The pattern observed for Hodgkin lymphoma in the HIV-infected population may reflect the fact that nearly all cases of this cancer in HIV-infected persons are related to Epstein-Barr virus (EBV) infection, which occurs more frequently in older individuals, whereas cases in the general population reflect cancers in both non–EBV-related Hodgkin

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**Figure 1.** Number and incidence rates of AIDS-defining cancers (ADCs) and non-AIDS-defining cancers (NADCs) in the United States, 1991 to 2005. Adapted from Shiels et al.<sup>1</sup>

lymphoma, which is more common in younger persons, and EBV-related Hodgkin lymphoma, which is more common in older persons.

### Higher Cancer Mortality in HIV-Infected Patients

A retrospective analysis assessed survival rates for incident prostate, anal, lung, and colorectal cancers, and Hodgkin lymphoma in 22,081 HIV-infected and 230,069 HIV-uninfected individuals enrolled in Kaiser Permanente in California.<sup>4</sup> Participants were matched for age, sex, clinic, and initial year of follow-up. The study showed that HIV-infected persons were diagnosed with anal, lung, and colorectal cancers at a somewhat earlier mean age than their

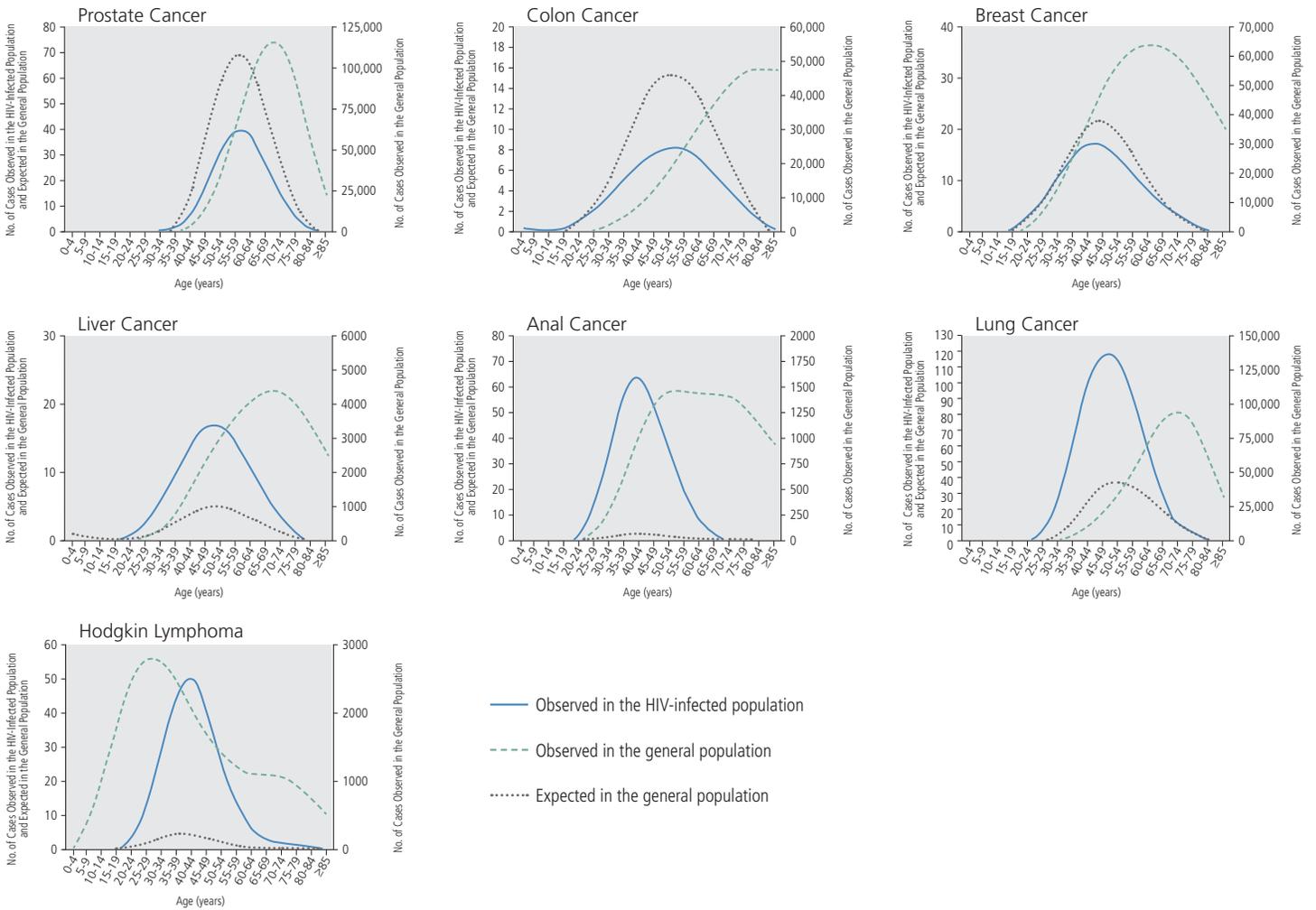
HIV-uninfected counterparts; were diagnosed with more advanced stages of lung cancer and Hodgkin lymphoma; and had statistically significantly poorer survival rates for Hodgkin lymphoma and lung and prostate cancers.

### Pathogenesis of NADCs

Although numerous factors are likely to be involved in the development of NADCs, many NADCs are associated with a viral pathogenesis. Anal cancer and oral squamous carcinoma are associated with human papillomavirus (HPV); Hodgkin lymphoma and pediatric leiomyosarcoma with EBV; Merkel cell carcinoma (which has a relative risk of approximately 20-fold in HIV-infected versus HIV-uninfected individuals) with

Merkel cell virus, a newly described DNA virus; and hepatocellular carcinoma with hepatitis B and C virus (HBV; HCV) infections. Among ADCs, Kaposi sarcoma is associated with human herpesvirus 8 (HHV-8), NHL with EBV and HHV-8, and invasive cervical carcinoma with HPV infection.

It is known that decreased immune surveillance and increased immune activation play a major role in cancer development. There is also a growing body of data, much of it from in vitro cell line studies, to suggest that HIV may have a direct role in perhaps activating cellular oncogenes or proto-oncogenes and inhibiting tumor suppressor genes. The NCI is conducting a large study comparing gene expression profiles in tumor specimens for a



**Figure 2.** Observed and expected cases of cancer, by age, in the HIV-infected and general populations in the United States, 1996 to 2007. Expected cases in the general population are modeled to match the age distribution of the HIV-infected population. Adapted from Shiels et al.<sup>3</sup>

variety of cancers in HIV-infected and HIV-uninfected persons,<sup>5</sup> and the findings should provide a clearer picture of which genes might be affected by HIV. Further, HIV has been found to induce genetic instability as manifested, for example, by a 6-fold higher number of microsatellite alterations in HIV-associated than in non-HIV-associated lung cancer.<sup>6</sup> Susceptibility to the effects of certain carcinogens may be greater in HIV-infected than in HIV-uninfected individuals, possibly due to the endothelial abnormalities associated with HIV infection, which may be permissive for tumor growth.

HIV-associated immunosenescence may also be associated with increased cancer risk. A number of reports indicate that the aging phenotype of immune markers first defined in Scandinavians

aged 80 years to 90 years is also common in younger HIV-infected individuals. Thus, increased CD8+ CD28- and CD4+ CD28- cells, shortened telomeres, increased CD31- cells (especially in the CD45RA+ naive T cell population), and increased CD56+ CD57+ cells are seen in HIV-infected patients compared with age-matched, HIV-uninfected patients. Such findings support the notion that HIV-infected persons experience more rapid immunologic aging, putting them at an increased risk for cancer.<sup>7-9</sup>

Predictors for NADCs in HIV-infected patients include advancing age (HR, 1.99 per 10 years;  $P < .001$ ), white versus black race (HR, 1.56;  $P = .02$ ), lower most-recent CD4+ cell count, smoking and other lifestyle behaviors, history of HBV infection, and socioeconomic disadvantage and limited

access to care. A recent report indicates a close correlation between lower CD4+ cell counts within the last 10 years and risk of virus-associated cancers. Antiretroviral therapy has been shown to be protective against ADCs (odds ratio, 0.21;  $P < .001$ ) but not against NADCs.<sup>10-12</sup>

## Cancer Screening

HIV-infected patients should be screened for cancer at earlier ages than HIV-uninfected patients given the differences in risk between the 2 groups, and screening should be performed more frequently for some cancer types. Guidelines from the American Cancer Society, NCI, and US Preventive Services Task Force indicate that cervical cancer screening should begin within

3 years of first vaginal intercourse or at 21 years of age and be performed every 1 year to 2 years.<sup>13-15</sup> For patients aged 30 years to 70 years with 3 normal Papanicolaou (Pap) test results, screening may be performed every 3 years. Prostate cancer screening should be discussed with a physician at age 50 years and a yearly digital rectal examination and individualized determination of prostate-specific antigen (PSA) testing performed. Breast cancer screening should consist of a clinical breast examination every 3 years beginning at age 20 years, yearly clinical breast examinations beginning at age 40 years, and yearly mammograms beginning at age 50 years. Colon cancer screening should begin at age 50 years and include flexible sigmoidoscopy every 5 years or colonoscopy every 10 years to age 75 years and yearly fecal occult blood testing. For other cancers, screening measures consist of periodic health examinations after age 20 years, with health counseling and oral, skin, lymph node, testicle, ovary, and thyroid examinations. Additional screening tests should be performed based on family history and other known cancer risk factors.

Routine cancer screening in HIV-infected patients appears to be conducted less frequently than age-appropriate standard-of-care screening is conducted in the general population for breast cancer (67% vs 79%) and colon cancer (56% vs 78%), and prostate biopsies are also performed less frequently in HIV-infected patients when indicated.<sup>16-18</sup> Some of this deficiency in cancer screening may reflect concerns over potentially higher false-positive rates among HIV-infected patients. For example, the NLST (National Lung Screening Trial) found a 20% reduction in lung cancer mortality among older smokers in the general population who were screened using low-dose helical computed tomography (CT) scan compared with those who underwent x-ray screening.<sup>19</sup> The false-positive rate was high, however, and might prove to be even higher in HIV-infected patients in whom pulmonary abnormalities are frequently encountered.

### Lung Cancer Screening

A Veterans Affairs Aging Cohort prospective substudy, EXHALE (Examinations of HIV Associated Lung Emphysema), compared rates of abnormal findings on a single, low-dose CT scan in 160 HIV-infected and 139 HIV-uninfected patients (85% and 81% of patients, respectively, were current or former smokers;  $P = .5$ ).<sup>20</sup> There were statistically significantly more men in the HIV-infected group than the HIV-uninfected group (98% vs 88%;  $P = .001$ ), and a small difference between the 2 groups in age (median age 54 years vs 52 years;  $P = .03$ ). There was no difference in racial or ethnic distribution (12% white, 72% black, and 16% Hispanic vs 20% white, 64% black, and 16% Hispanic;  $P = .41$ ), pack-years of smoking (median 26 years vs 22 years;  $P = .4$ ), or presence of chronic obstructive pulmonary disease, emphysema, or chronic bronchitis (22% vs 24%;  $P = .4$ ). CD4+ cell count was  $< 200/\mu\text{L}$  in 14% and  $> 200/\mu\text{L}$  in 86% of the HIV-infected group, and 84% of the HIV-infected group was on antiretroviral therapy.

There were no statistically significant differences between the HIV-infected and HIV-uninfected groups in presence of pulmonary nodules (48% vs 48%;  $P = .9$ ), median number of nodules (2 vs 1;  $P = .2$ ), suspicion of cancer (4% vs 3%;  $P = .8$ ), pleural effusion (0% vs 0.7%;  $P = .5$ ), ground glass infiltrates (15% vs 14%;  $P = .9$ ), bronchiectasis (6% vs 6%;  $P = .8$ ), or granulomas (24% vs 18%;  $P = .2$ ). Borderline statistically significant differences were observed between the HIV-infected and HIV-uninfected groups in emphysematous changes (41% vs 30%;  $P = .05$ ) and lymphadenopathy (13% vs 6.5%;  $P = .1$ ). Follow-up was recommended for 23% of the HIV-infected group versus 30% of the HIV-uninfected group ( $P = .2$ ) and resulted in a lung cancer diagnosis in 3 subjects in the HIV-infected group and 1 subject in the HIV-uninfected group (2% vs 0.7%). It remains unclear whether routine CT screening for lung cancer would provide much benefit. At present, it appears that CT findings would be contaminated by the presence of

many abnormalities, perhaps leading to additional evaluation that might not necessarily assist in early diagnosis and could ultimately prove to be harmful.

### Anogenital Dysplasia Screening

Anal cancer is particularly common in HIV-infected men who have sex with men, although it also develops in HIV-infected women, and it is one of several cancers with an increasing incidence in the antiretroviral therapy era. Currently, there are no national or international guidelines for anal cancer screening other than the New York State Department of Health AIDS Institute clinical guidelines for anal dysplasia and cancer,<sup>21</sup> which do not provide guidance on what to do in the case of positive screening results. Many experts recommend yearly cervical and anal Pap smears, with colposcopy or high-resolution anoscopy and biopsy of any suspicious lesions, and follow-up every 6 months in patients with abnormalities. A number of cervical cancer screen-and-treat programs are now operating in resource-limited settings.<sup>22,23</sup>

AMC-052 (AIDS Malignancy Consortium Protocol 052) evaluated anal cancer screening as part of an HPV vaccination protocol and showed that a large percentage of HIV-infected men tested negative for HPV types associated with cancer,<sup>24</sup> indicating that vaccination would benefit this population. At 7 months, after 3 vaccine doses, geometric mean anti-HPV antibody levels were 357 mMU/mL, 525 mMU/mL, 1139 mMU/mL, and 181 mMU/mL for HPV types 6, 11, 16, and 18, respectively. Although these antibody levels are not as high as those achieved in HIV-uninfected men, they are still likely to be protective.

With regard to dysplasia treatment, a 16-week randomized trial evaluated the use of topical imiquimod (thrice weekly), topical 5-fluorouracil (5-FU; twice weekly), and electrocautery (monthly) in 156 HIV-infected men with anal intraepithelial neoplasia (AIN), 63% of whom had high-grade AIN (HGAIN).<sup>25</sup> Using a modified intent-to-treat analysis, at 4 weeks after completing treatment, complete response rates were 24%

in those treated with imiquimod, 17% in those treated with 5-FU, and 39% in those treated with electrocautery ( $P = .027$ ). Relapse rates at 6 months were 19%, 38%, and 14%, and at 48 weeks were 47%, 50%, and 43%, respectively, suggesting an advantage to electrocautery in terms of complete response rates, but relapses were equally high in all groups by 48 weeks. Serious, grade 3 or 4 adverse events were more common in the imiquimod treatment group than in the 5-FU or electrocautery treatment groups (43%, 27%, and 18%, respectively;  $P = .019$ ).

The AMC has been examining the use of infrared coagulation techniques pioneered by Palefsky and colleagues at the University of California San Francisco and has observed higher response rates (62%) and a 1-year recurrence or persistence rate of less than 38%.<sup>26</sup> Although optimal treatment is still being identified, it seems clear that effective early intervention in AIN can reduce anal cancer incidence.

## Cancer Prevention

Smoking cessation is a high-priority measure for cancer prevention in any population, as is the use of sunscreen and avoiding overexposure to the sun. In HIV-infected patients, obtaining a complete family history for malignancies is important and a high index of suspicion for cancer should be maintained. Plasma HIV RNA levels should be maximally suppressed with effective antiretroviral therapy, and HCV or HBV should be treated in individuals with active HIV/HCV or HIV/HBV coinfections. Other measures for cancer prevention in HIV-infected patients include vaccination against HBV and HPV. Annual cervical and anal Pap tests, and regular screening with high-resolution anoscopy may be indicated. Breast, prostate, and colon cancer screening should be performed according to relevant guidelines for the general population.

## Conclusion

As the HIV-infected population ages with persistent immune abnormalities, cancers are increasing in number. The risk

of NADCs is high, with lung, anal, and liver cancers and Hodgkin lymphoma accounting for most new cases. The risk for colon, breast, and prostate cancers is lower in the HIV-infected population than in the general population. Hodgkin lymphoma incidence is similar overall, but higher in older HIV-infected individuals, and may reflect the lack of a younger age peak, which is seen in the general US population, as almost all cases of Hodgkin lymphoma in the HIV-infected population appear to be related to EBV infection. At a minimum, age- and sex-appropriate cancer screening should be performed in all patients, and patients should be counseled on measures to reduce cancer risk. Only through prospective clinical trials can HIV-specific cancer prevention strategies be effectively evaluated. 

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### Additional Suggested Reading

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1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated April 2010. Available at <http://www.icmje.org>. Accessed July 10, 2014.



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