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Topics in Antiviral Medicine™

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On completion of this activity, participants will be able to:

- Choose from among available initial antiretroviral regimens and list some investigational antiretroviral drugs currently in the pipeline
- Describe the effects of human papillomavirus infection in HIV-infected women as well as guidelines for cervical cancer screening in this population
- Recognize the risk factors for cardiovascular disease in the HIV-infected population and the potential role of statin therapy, and describe the design and goals of the REPRIEVE study

Intended Audience

This enduring material is designed for physicians and other health care practitioners who are actively involved in the medical care of people with HIV infection.

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

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Perspective

Choosing Initial Antiretroviral Therapy: Current Recommendations for Initial Therapy and Newer or Investigational Agents

There is general consistency among US and European guidelines regarding the initiation of antiretroviral therapy for HIV-infected individuals. Recent and ongoing trials comparing regimens may lead to reevaluation of initial treatment choices. The choice of antiretroviral regimen will also likely be affected by development, evaluation, and availability of newer drugs. This article reviews currently recommended regimens and characteristics of selected current investigational drugs, including the nucleotide analogue reverse transcriptase inhibitor tenofovir alafenamide, the nonnucleoside reverse transcriptase inhibitor doravirine, the integrase strand transfer inhibitor cabotegravir, the HIV entry inhibitor BMS-663068, and the HIV maturation inhibitor BMS-955176. This article summarizes a presentation by Roy M. Gulick, MD, MPH, at the IAS–USA continuing education program, Improving the Management of HIV Disease, *held in New York, New York, in March 2015 and September 2015.*

Keywords: HIV, antiretroviral drugs, initial therapy, tenofovir, TAF, doravirine, cabotegravir, BMS-663068, BMS-955176, CD4 attachment inhibitor, HIV maturation inhibitor

As of late 2015, 29 antiretroviral drugs are approved by the US Food and Drug Administration (FDA) for the treatment of HIV infection. Over the years, antiretroviral drugs have evolved to have greater potency, safety, and convenience in initial antiretroviral therapy regimens. A recent systematic analysis by Lee and colleagues of 114 antiretroviral therapy trials with intent-to-treat analyses and up to 3 years of follow-up through 2012 showed that the proportion of participants who achieved an undetectable viral load level on their initial antiretroviral treatment increased from 43% in the mid-1990s to more than 80% by 2010.[1] The same analysis showed that the rate of participant discontinuations attributable to intolerance or toxic effects decreased from 14% to 4%, with rates of 3% or lower reported in more recent studies.[2-4] Today, rates of virologic suppression of 90% or higher are being achieved among HIV-infected individuals in clinical trials and in clinical practice.[4,5]

An example of the improvement of antiretroviral therapy in clinical practice is provided by findings in British Columbia, Canada, where all HIV-infected individuals in the province receive treatment from a single site. The proportion of individuals receiving any antiretroviral therapy (not only initial) with plasma HIV RNA levels below 50 copies/mL increased from 65% in 2000 to 87% in 2008.[6] An informal assessment survey of the HIV clinic at New York–Presbyterian/Weill Cornell Medical Center in New York, New York, indicated that approximately 90% of patients taking antiretroviral therapy had undetectable viral load levels.

Dr Gulick is Gladys and Roland Harriman Professor of Medicine and Chief of the Division of Infectious Diseases at Weill Medical College of Cornell University in New York, New York. He is a volunteer member of the Board of Directors of the IAS–USA.

What to Start

Initiation of antiretroviral therapy is currently recommended for essentially all HIV-infected adults regardless of CD4+ cell count or viral load.[7-11] Updated guidelines from the US Department of Health and Human Services (DHHS) for initial antiretroviral therapy recommend 1) an integrase strand transfer inhibitor (InSTI)-containing regimen of dolutegravir, abacavir, and lamivudine; dolutegravir, tenofovir disoproxil fumarate (TDF), and emtricitabine; cobicistat-boosted elvitegravir, TDF, and emtricitabine; cobicistat-boosted elvitegravir, tenofovir alafenamide (TAF), and emtricitabine; or raltegravir, TDF, and emtricitabine; or 2) a protease inhibitor (PI)-containing regimen of ritonavir-boosted darunavir, TDF, and emtricitabine (Table 1).[8]

Current guidelines from the IAS–USA, the European AIDS Clinical Society, and the British HIV Association regarding which regimens to use for initial antiretroviral treatment variably recommend TDF and emtricitabine or abacavir and lamivudine with a third drug chosen from the nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs)

Table 1. Recommended Initial Antiretroviral Regimens From US Department of Health and Human Services Guidelines

InSTI-Based Regimens	PI-Based Regimen
- Dolutegravir, abacavir, and lamivudine[a] - Dolutegravir, tenofovir disoproxil fumarate, and emtricitabine[a] - Elvitegravir boosted with cobicistat plus tenofovir disoproxil fumarate and emtricitabine - Elvitegravir boosted with cobicistat plus tenofovir alafenamide and emtricitabine - Raltegravir, tenofovir disoproxil fumarate, and emtricitabine[a]	- Darunavir boosted with ritonavir plus tenofovir disoproxil fumarate and emtricitabine[a]

Abbreviations: InSTI, integrase strand transfer inhibitor; PI, protease inhibitor. Adapted from US Department of Health and Human Services.[8]

[a]Lamivudine and emtricitabine may be substituted for one another in these regimens.

Table 2. Alternative Initial Antiretroviral Regimens From US Department of Health and Human Services Guidelines

NNRTI-Based Regimens	PI-Based Regimens
- Efavirenz, tenofovir disoproxil fumarate, and emtricitabine[a] - Rilpivirine, tenofovir disoproxil fumarate, and emtricitabine[a]	- Atazanavir boosted with cobicistat plus tenofovir disoproxil fumarate and emtricitabine[a] - Atazanavir boosted with ritonavir plus tenofovir disoproxil fumarate and emtricitabine[a] - Darunavir boosted with either cobicistat or ritonavir plus abacavir and lamivudine[a] - Darunavir boosted with cobicistat plus tenofovir disoproxil fumarate and emtricitabine[a]

Abbreviations: NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor. Adapted from Department of Health and Human Services.[8]

[a]Lamivudine and emtricitabine may be substituted for one another in these regimens.

efavirenz and rilpirivine, the ritonavir-boosted PIs atazanavir and darunavir, or the InSTIs dolutegravir, elvitegravir, and raltegravir.[7,9,10] World Health Organization guidelines for antiretroviral treatment in resource-limited regions recommend TDF in combination with emtricitabine or lamivudine plus efavirenz.[11] Regimens categorized as alternative by the DHHS are listed in Table 2.[8]

Recent results from comparative trials of recommended initial regimens in HIV-infected, treatment-naive participants may help practitioners choose from among recommended initial regimens. In the SINGLE trial, which compared once-daily abacavir and lamivudine plus dolutegravir with TDF, emtricitabine, and efavirenz, and in the FLAMINGO trial, which evaluated the once-daily regimens of dual nucleos(t)-ide analogue reverse transcriptase inhibitors (nRTIs) plus dolutegravir or ritonavir-boosted darunavir, dolutegravir-containing therapy was statistically superior in terms of viral suppression rates and appeared to be better tolerated.[2,3] In the SPRING-2 trial, which allowed TDF and emtricitabine or abacavir and lamivudine plus either once-daily dolutegravir or twice-daily raltegravir, dolutegravir-containing regimens were statistically noninferior.[12]

In the AIDS Clinical Trials Group (ACTG) 5257 trial, which evaluated TDF and emtricitabine plus ritonavir-boosted atazanavir, ritonavir-boosted darunavir, or raltegravir, the raltegravir-containing regimen was superior to the 2 PI-containing regimens; additionally, the darunavir-containing regimen was superior to the atazanavir-containing regimen, owing primarily to better tolerability (mostly related to gastrointestinal symptoms and hyperbilirubinemia).[4] These data suggest that currently recommended initial antiretroviral regimens may evolve further, and this may be reflected in future updated guidelines.

Newer or Investigational Antiretroviral Agents

Characteristics of the recently approved nRTI TAF, the investigational NNRTI doravirine (also referred to as DOR), the investigational InSTI cabotegravir (also referred to as CAB), the investigational entry inhibitor BMS-663068, and the investigational maturation inhibitor BMS-955176 are discussed below.

Tenofovir Alafenamide

Highly desirable characteristics for a new nRTI are fewer long-term toxic effects and activity against resistant virus. The investigational nRTI TAF, like its predecessor TDF, is a prodrug of tenofovir. TDF is converted to tenofovir in plasma and then converted to tenofovir diphosphate in lymphoid cells, whereas TAF remains in prodrug form until it enters lymphoid cells, where it is also converted to tenofovir diphosphate. When TAF was developed, it was hoped that it would be associated with more efficient delivery to lymphocytes and with less drug delivery to kidney and bone, possibly decreasing toxic effects.

Combined results of 2 identically designed double-blind phase III noninferiority studies that compared TAF with TDF plus cobicistat-boosted elvitegravir and emtricitabine were recently published. Study 104 was conducted in North America, Europe, and Asia, and Study 111 was conducted in North America, Europe, and Latin America.[5] The combined efficacy analysis was prespecified. Of 1733 treatment-naive participants with HIV RNA levels of at least 1000 copies/mL and estimated glomerular filtration rates of at least 50 mL/min, 866 were randomly assigned to receive once-daily TAF and 867 were randomly assigned to receive once-daily TDF. The primary end point was the proportion of participants with HIV RNA level below 50 copies/mL; the noninferiority margin was 12% based on an FDA snapshot analysis at week 48.

Combined analysis at week 48 showed that 92% of those who received TAF versus 90% of those who received TDF achieved virologic suppression; 4% and 4%, respectively, experienced virologic failure, and for 4% and 6%, respectively, no data were available. The treatment difference between TAF and TDF was +2.0%, with a 95% confidence interval of -0.7% to +4.7% (that excluded -12.0%), thus meeting the criteria for noninferiority. Analyses of baseline viral load and CD4+ cell count subgroups showed no difference in suppression rates between study groups. In addition, TAF was associated with fewer nephrotoxic effects and less bone mineral density loss. TAF exposure has been found to substantially increase when TAF is coadministered with ritonavir-boosted atazanavir, lopinavir, or darunavir, whereas little effect has been observed when TAF is coadministered with dolutegravir or rilpivirine.[13] There are plans for fixed-dose formulations of emtricitabine 200 mg and TAF 10 mg for concomitant use with boosted PIs or elvitegravir or TAF 25 mg for concomitant use with other InSTIs and NNRTIs. TAF was approved by the FDA in November 2015.

Doravirine

Desirable characteristics for a new NNRTI include fewer toxic effects and drug-drug interactions, better tolerability, and

activity against NNRTI-resistant virus strains. The investigational NNRTI doravirine is active in vitro against HIV with NNRTI resistance–associated mutations, including K103N, Y181C, G190A, E101K, E138K, and K103N/Y181C. Doravirine is metabolized by cytochrome P450 3A4 (CYP3A4) but is not a CYP450 inhibitor or inducer, suggesting a lower potential for drug-drug interactions.[14] However, interactions with rifampin have been observed, and coadministration of rifampin and doravirine reduces doravirine exposure by more than 57%.[15] In a study of HIV-seronegative men given single or repeated doses of doravirine, no rash or central nervous system events were reported and pharmacokinetics supported once-daily dosing.[16]

In a phase Ib study of 18 treatment-naive individuals, reductions of HIV RNA levels of approximately 1.5 $\log_{10}$ copies/mL were observed with daily doses of doravirine 25 mg and doravirine 200 mg given for 7 days.[17] In a phase IIb study, treatment-naive individuals were randomly assigned to receive TDF and emtricitabine plus efavirenz (n = 42) or doravirine at 25 mg (n = 40), 50 mg (n = 42), 100 mg (n = 40), or 200 mg (n = 41). At 24 weeks, an HIV RNA level of less than 40 copies/mL was achieved in 80% , 76% , 71% , and 78% of those who received doravirine, respectively, (overall 76%) and in 64% of those who received efavirenz.[18] At 48 weeks, the response rates were 73%, 72%, 76%, and 83% for those who received doravirine, respectively, and 71% for those who received efavirenz.[19] Nausea was reported in 8% of those who received doravirine and 2% of those in the control group, fatigue in 7% and 5%, respectively, and diarrhea in 5% and 10%, respectively. Doravirine 100 mg was selected for phase III testing. At 48 weeks, the rates of toxic effects in the central nervous system were greater among those who received efavirenz than among those who received doravirine 100 mg (44% vs 22%, respectively; $P < .001$), including rates of dizziness (28% vs 9%, respectively) and abnormal dreams (17% vs 6%, respectively); rates of insomnia (3% vs 6%, respectively) and nightmares (8% vs 6%, respectively) were similar. Phase III studies are in progress.

Cabotegravir

A desirable characteristic of a new InSTI is less frequent dosing. The investigational InSTI cabotegravir has a similar chemical structure and resistance profile to dolutegravir but may allow for less frequent parenteral dosing. A new investigational nanotechnologic formulation of cabotegravir may be subcutaneously or intramuscularly injected and has a half-life of 21 days to 50 days, supporting monthly or even quarterly dosing (Figure 1).[20] Adverse effects were limited to mild injection-site reactions when single doses of this formulation were studied, although nodules were observed with subcutaneous dosing.

The pairing of long-acting parenteral drugs (ie, cabotegravir and rilpivirine) as maintenance antiretroviral therapy that could be given monthly is currently being investigated. The LATTE-1 (Long-Acting Antiretroviral Treatment Enabling –1) study assessed the potential of maintenance therapy with oral forms of cabotegravir and rilpivirine.[21] In the study, 243 treatment-naive participants were randomly assigned to receive 2 nRTIs plus daily oral cabotegravir at 10 mg, 30 mg, or 60 mg or efavirenz during an induction phase. For individuals who received cabotegravir, if HIV RNA level was less than 50 copies/mL at 24 weeks, the 2 nRTIs were replaced by daily oral rilpivirine 25 mg. Overall, approximately 80% of participants who received cabotegravir achieved virologic suppression at 24 weeks, and these responses were maintained to 96 weeks with oral cabotegravir plus oral rilpivirine. The LATTE-2 study is currently evaluating oral cabotegravir during induction therapy and parenteral cabotegravir and rilpivirine as maintenance therapy.

BMS-663068

Inhibition of attachment of HIV to CD4+ cells would add a new mechanism of action to HIV treatment options. BMS-663068 is an investigational prodrug of BMS-626529 that inhibits virus from binding to CD4+ cells by binding to HIV envelope glycoprotein 120 (gp120). Pharmacokinetic data support once- or twice-daily dosing of BMS-663068 without boosting. Reduced baseline susceptibility caused by polymorphisms in gp120 was observed in 12% of individuals' virus via retrospective measurement of pretreatment 50% inhibitory concentration (IC_{50}). In phase I testing, BMS-663068 was associated with an approximately 1.5 $\log_{10}$ reduction in HIV RNA level.[22] In a phase IIb study, 251 treatment-experienced participants who had an IC_{50} of the prodrug BMS-626529 of less than 100 nM received TDF and raltegravir plus BMS-663068 400 mg or 800 mg twice daily, BMS-663068 600 mg or 1200 mg once daily, or ritonavir-boosted atazanavir. At week 48, an HIV RNA level below 50 copies/mL was achieved in 61% to 82% of those who

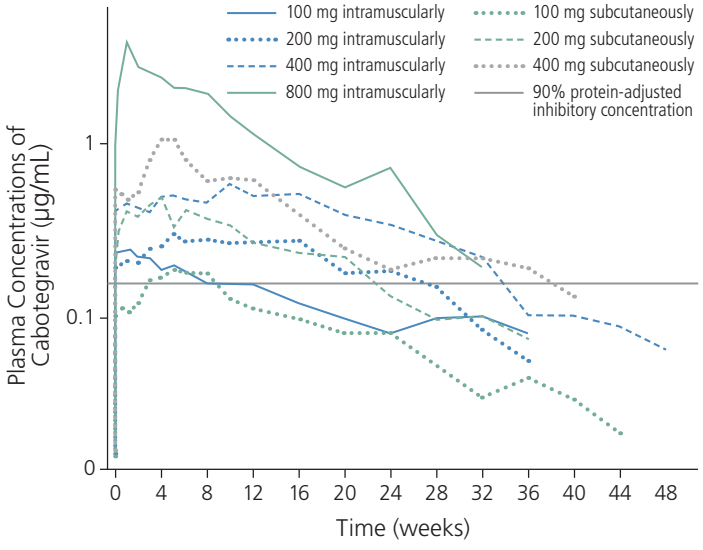

Figure 1. Mean plasma concentration–time profiles following administration of the single-dose, long-acting parenteral formulation of the investigational integrase strand transfer inhibitor cabotegravir. Adapted from Spreen et al.[20]

received BMS-663068 and in 71% of those who received ritonavir-boosted atazanavir, with no differences observed in response measured by baseline viral load or CD4+ cell count.[23] BMS-663068 600 mg twice daily was selected for phase III evaluation, and heavily treatment-experienced participants are currently being enrolled in clinical trials.[24]

BMS-955176

Inhibition of viral maturation would also be a novel mechanism of action in HIV treatment. A desirable characteristic of a maturation inhibitor is the absence of baseline polymorphisms that confer resistance. BMS-955176 is an oral, second-generation, investigational maturation inhibitor that acts by binding to the HIV Gag polyprotein. It exhibits greater potency and Gag polymorphism coverage than the investigational, first-generation maturation inhibitor bevirimat for which baseline resistance was seen in approximately half of individuals. Pharmacokinetics of BMS-955176 support once-daily dosing.[25]

In a dose-escalation study of individuals who were naive to PI-containing and maturation inhibitor–containing treatment, reductions in HIV RNA level of approximately 1.5 $\log_{10}$ were achieved with 10 days of treatment with the highest doses of BMS-955176.[25] No serious adverse events, grade 3 or 4 adverse events, or treatment-related discontinuations were observed. BMS-955176 has moved into phase II testing.

Presented by Dr Gulick in March 2015 and September 2015. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Gulick in November 2015.

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Special Contribution

2015 Update of the Drug Resistance Mutations in HIV-1

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The 2015 edition of the IAS–USA drug resistance mutations list updates the figures last published in July 2014. The mutations listed are those that have been identified by specific criteria for evidence and drugs described. The figures are designed to assist practitioners in identifying key mutations associated with resistance to antiretroviral drugs and, therefore, in making clinical decisions regarding antiretroviral therapy.

The 2015 edition of the IAS–USA drug resistance mutations list updates the figures last published in July 2014.[1] The following mutations have been added to the bars for the integrase strand transfer inhibitors: Q148R, N155H, and R263K for dolutegravir, and R263K for elvitegravir and raltegravir.[2-5] The G140S mutation for dolutegravir is no longer bold, and the Q148H/K mutations for elvitegravir are now bold.[6]

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 drug resistance–associated mutations for HIV clinical practitioners. The group reviews new data on HIV drug resistance to maintain a current list of mutations associated with clinical resistance to HIV-1. 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 as well as any drugs available in expanded access programs are included (listed in alphabetic 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 emerges most commonly to lamivudine or emtricitabine or nonnucleoside analogue reverse transcriptase inhibitors).

The absence of detectable viral resistance after treatment failure may result from any combination of the following factors: the presence of drug-resistant minority viral populations, a prolonged interval between the time of antiretroviral drug discontinuation and genotypic testing, nonadherence to medications, laboratory error, lack of current knowledge of the association of certain mutations with drug resistance, the occurrence of relevant mutations outside the regions

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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[7] and 2014 IAS–USA panel recommendations for antiretroviral therapy.[8] Updates are posted periodically at www.iasusa.org.

Comments

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

Reprint Requests

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

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

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

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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)[a]

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

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

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

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

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

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

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

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

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

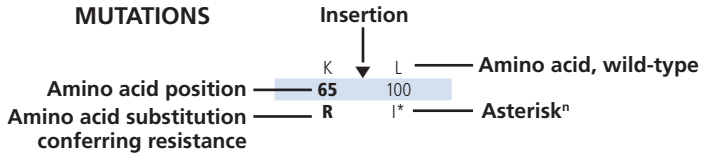
	L	K	K	V	V	Y	Y	G	P	M
Efavirenz	**100**	**101**	**103**	**106**	**108**	**181**	**188**	**190**	**225**	**230**
	I	**P**	**N**	**M**	**I**	**C**	**L**	**S**	**H**	**L**
			S			**I**		**A**		

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

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

	L	K	E	V	Y	Y	H	F	M
Rilpivirine[o]	**100**	**101**	**138**	**179**	**181**	**188**	**221**	**227**	**230**
	I	**E**	**A**	**L**	**C**	**L**	**Y**	**C**	**I**
		P	**G**		**I**				**L**
			K		**V**				
			Q						
			R						

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



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

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

MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

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

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

	T	L	E	T	F	E	G	Y	S	Q	N	R
Dolutegravir[aa]					121	138	140			**148**	155	263
					Y	A	A			**H**	H	K
						K	S			**R**		
Elvitegravir[bb]	**66**		**92**	97	**121**				**147**	**148**	**155**	263
	I		**Q**	A	**Y**				**G**	**H**	**H**	K
	A		G							**K**		
	K									**R**		
Raltegravir[cc]		74	92	97	**121**	138	140	**143**		**148**	**155**	263
		M	Q	A	**Y**	A	A	**R**		**H**	**H**	K
						K	S	**H**		**K**		
								C		**R**		

User Notes

a. Some nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) mutations, like T215Y and H208Y,[1] may lead to viral hypersusceptibility to nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs), including etravirine,[2] in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens (nevirapine or efavirenz) in NNRTI-naive individuals,[3-7] although no clinical data exist for improved response to etravirine in NNRTI-experienced individuals. Mutations at the C-terminal reverse transcriptase domains (amino acids 293-560) outside of regions depicted on the figure bars may prove to be important for nRTI and NNRTI HIV-1 drug resistance. The clinical relevance of these connection domain mutations arises mostly in conjunction with thymidine analogue–associated mutations (TAMs) and M184V and they have not been associated with increased rates of virologic failure of etravirine or rilpivirine in clinical trials.[8-10] 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.[11,12]

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 Food and Drug Administration (FDA) when present with 1 or more TAMs at codons 41, 210, or 215.[13] 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.[13] 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.[14] The degree to which cross-resistance is observed depends on the specific mutations and number of mutations involved.[15-18]

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.[19-21]

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.[22,23]

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.[22,24,25] 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.[26] The presence of K70R or M184V alone does not decrease virologic response to didanosine.[27]

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.[28,29]

j. The presence of M184V appears to delay or prevent emergence of TAMs.[30] This effect may be overcome by an accumulation of TAMs or other mutations.

k. The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations at codon 215 that confer increased risk of virologic failure of zidovudine or stavudine in antiretroviral-naive patients.[31,32] The T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine.[33]

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

m. There is no evidence for the utility of efavirenz, nevirapine, or rilpivirine in patients with NNRTI resistance.[37]

n. Resistance to etravirine has been extensively studied only in the context of coadministration with ritonavir-boosted darunavir. 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.[38-40] Asterisks (*) are used to emphasize higher relative weights with regard to reduced susceptibility and reduced clinical response compared with other etravirine mutations.[41] The single mutations L100I*, K101P*, and Y181C*/I*/V* reduce clinical utility. The presence of K103N alone does not affect etravirine response.[42] Accumulation of several mutations results in greater reductions in susceptibility and virologic response than do single mutations.[43-45]

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).[46-48] A 16th mutation, Y188L, reduces rilpivirine susceptibility 6 fold.[48] K101P and Y181I/V reduce rilpivirine susceptibility approximately 50 fold and 15 fold, respectively, but are not commonly observed in patients receiving rilpivirine.[49-51] Mutations at position 138 (most notably 138A) may occur as natural polymorphisms, especially in non-B subtypes.[52] 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–associated 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.[51,53-55] The combinations of reverse transcriptase–associated mutations L100I plus K103N/S and L100I plus K103R plus V179D were strongly associated with reduced susceptibility to rilpivirine. However, for isolates harboring the K103N/R/S or V179D as single mutations, no reduction in susceptibility was detected.[48,56]

p. Often, numerous mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI).[57] 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 PIs and may emerge before mutations in protease do.[58] A large proportion of virus samples from patients with confirmed virologic failure on a PI-containing regimen is not found to have PI resistance–associated mutations. Preliminary data from recent studies suggest that several mutations in the Gag protein[59] and in the cytoplasmic tail of the Env protein[58] 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 doses 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.[60]

t. HIV-1 RNA response to ritonavir-boosted darunavir correlates with baseline susceptibility and the presence of several specific PI resistance–associated 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 ritonavir-boosted darunavir were shown in 2 data sets independently.[61,62] Some of these mutations appear to have a greater effect on susceptibility than others (eg, I50V vs V11I). The presence at baseline of 2 or more of the substitutions V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V was associated with a decreased virologic response to ritonavir-boosted darunavir.[63]

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 ritonavir-boosted lopinavir.[64,65] The product information states that accumulation of 7 or 8 mutations confers resistance to the drug.[66] However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I, are associated with high-level resistance.[67-69] The addition of L76V to 3 PI resistance–associated mutations substantially increases resistance to ritonavir-boosted lopinavir.[60]

w. In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI resistance–associated mutations.[70]

x. 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.[71-73]

y. The activity of CC chemokine receptor 5 (CCR5) antagonists is limited to patients with virus that uses only CCR5 for entry (R5 virus). Viruses that use both CCR5 and CXC chemokine receptor 4 (CXCR4; termed dual/mixed [D/M] virus) or only CXCR4 (X4 virus) do not respond to treatment with CCR5 antagonists. Virologic failure of these drugs is frequently 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.[74] 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[75]; the clinical significance of such mutations is not yet known.

z. 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. Mutation R263K can be selected in vivo during treatment with dolutegravir and raltegravir and results in a 2- to 5-fold reduction in susceptibility to dolutegravir, elvitegravir, and raltegravir.[76-81]

aa. Several mutations are required in HIV integrase to confer high-level resistance to dolutegravir.[82] Cross-resistance studies with raltegravir- and elvitegravir-resistant viruses indicate that Q148H/R 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 [83] and reduced virologic suppression in patients.[84-87]

bb. Seven elvitegravir codon mutations have been observed in integrase strand transfer inhibitor treatment–naive and –experienced patients in whom therapy is failing.[88-94] T97A results in only a 2-fold change in elvitegravir susceptibility and may require additional mutations for resistance.[93,94] The sequential use of elvitegravir and raltegravir (in either order) is not recommended because of cross-resistance between these drugs.[93]

cc. Raltegravir failure is associated with integrase mutations in at least 3 distinct, but not exclusive, genetic pathways defined by 2 or more mutations including (1) a signature (major) mutation at Q148H/K/R, N155H, or Y143R/H/C; and (2) 1 or more additional minor mutations. Minor mutations described in the Q148H/K/R pathway include L74M plus E138A, E138K, or G140S. The most common mutational pattern in this pathway is Q148H plus G140S, which also confers the greatest loss of drug susceptibility. Mutations described in the N155H pathway include this major mutation plus either L74M, E92Q, T97A, E92Q plus T97A, Y143H, G163K/R, V151I, or D232N.[95] The Y143R/H/C mutation is uncommon.[96-100] E92Q alone reduces susceptibility to elvitegravir more than 20 fold and causes limited (< 5 fold) cross-resistance to raltegravir.[90,101-103] N155H mutants tend to predominate early in the course of raltegravir failure, but are gradually replaced by viruses with higher resistance, often bearing mutations G140S plus Q148H/R/K, with continuing raltegravir treatment.[96]

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Perspective

Screening for Human Papillomavirus–Associated Cervical Disease in HIV-Infected Women

HIV-infected women have higher rates of persistence of human papillomavirus (HPV) infection, of abnormal cervical cytology results, and of cervical cancer than uninfected women. It is currently recommended that HIV-infected, sexually active women have a Papanicolaou (Pap) test performed at the time of initial diagnosis of HIV infection, followed by annual Pap testing if the previous test result is normal. Women whose test results show abnormalities greater than atypical squamous cells of undetermined significance (ASCUS) should be referred for colposcopy. Those with ASCUS should undergo immediate colposcopy or repeat cervical cytology in 6 months to 12 months, and those whose repeat cervical cytology results show ASCUS or greater abnormalities should undergo colposcopy. Recent findings indicate that screening intervals can be lengthened for HIV-infected women whose Pap test results are persistently normal and who are engaged in routine care, and that HPV DNA testing may have a role in screening. This article summarizes a presentation by Marla J. Keller, MD, at the IAS–USA continuing education program, Improving the Management of HIV Disease, *held in Atlanta, Georgia, in March 2015.*

Keywords: HIV, human papillomavirus, HPV, cervical cancer screening, cervical cytology, oncogenic HPV DNA testing

More than 150 types of human papillomavirus (HPV) have been identified, including approximately 40 that can infect the cervix and approximately a dozen that are carcinogenic. HPV-16 accounts for 50% to 55% of all cases of invasive cervical cancer worldwide, and HPV-18 accounts for an additional 10% to 15%. Cervical cancer represents approximately 10% of all cancers that affect women worldwide, and virtually all are attributable to HPV.

Cervical cancer is the third most common type of cancer among women worldwide, with approximately 530,000 new cases and 275,000 related deaths occurring each year. Approximately 12,000 new cases of cervical cancer occur each year in the United States. The risk of cervical cancer, an AIDS-defining malignancy, is increased several fold in HIV-infected women.

Human Papillomavirus Infection in HIV-Infected Women

Clearance of HPV infection is extremely common. Typically, it takes decades for a high-grade squamous intraepithelial lesion (HSIL) to grow and become invasive. Before cervical precancer or cancer can develop, there must be persistent oncogenic HPV infection and an accumulation of genetic changes over time. Thus, a woman with a normal Papanicolaou (Pap) test result who does not have oncogenic HPV infection should have a low risk of developing cervical precancer or cancer for several years, regardless of her HIV serostatus. However, HIV-infected women have greater persistence of HPV infection compared to HIV-uninfected women. Persistence rates are 2- to 6-fold higher for any HPV type and 6-fold higher for HPV-16 and HPV-18.[1,2]

In the WIHS (Women's Interagency HIV Study), HIV-infected and uninfected women have semiannual Pap testing, polymerase chain reaction (PCR) testing for more than 40 types of HPV, and colposcopy when indicated. Data on approximately 1900 HIV-infected women and 500 uninfected women who were observed for at least 10 years showed a cumulative risk of 77% and 50%, respectively, of having an abnormal cytology result and a cumulative risk of 4% and 1%, respectively, of having HSILs.[3] Overall, HIV-infected women have greater diversity of HPV types; greater prevalence of numerous types of HPV; greater preponderance of types of HPV other than HPV-16 and HPV-18; higher prevalence of low-grade squamous intraepithelial lesions (LSILs) and HSILs; rates of progression of HPV infection that are more rapid; lower rates of spontaneous regression of HPV infection; and higher rates of persistent or recurrent HPV infection following treatment.

Overall, HIV-infected women have a 5.4-fold higher risk for cervical cancer and a 6.8-fold higher risk for anal cancer than uninfected women. Longer duration of HPV persistence, longer life expectancy owing to effective antiretroviral therapy, and greater proportions of women entering age groups in which cervical cancer rates reach their peak contribute to the excess risk of cervical cancer.[4] Increased immunosuppression in HIV-infected women is associated with increased risk for cervical cancer. As shown in the Figure, the cervical cancer rate is higher in HIV-infected women with CD4+ cell counts below 200/µL than in HIV-infected women with CD4+ cell counts above 200/µL and uninfected women.[5,6]

The incidence of cervical cancer in HIV-infected women has not decreased appreciably since the introduction of antiretroviral therapy. However, data indicate that HIV-infected women who are adherent to antiretroviral therapy experience substantial reductions in the burdens of HPV infection and SILs. A study in the WIHS cohort showed a 40% reduction in prevalence of oncogenic HPV infections, a 50% reduction in incidence of oncogenic HPV infections, and faster clearance of oncogenic HPV-related SILs after initiation of antiretroviral therapy.[7] Benefits of antiretroviral therapy were reduced in women who were less adherent.

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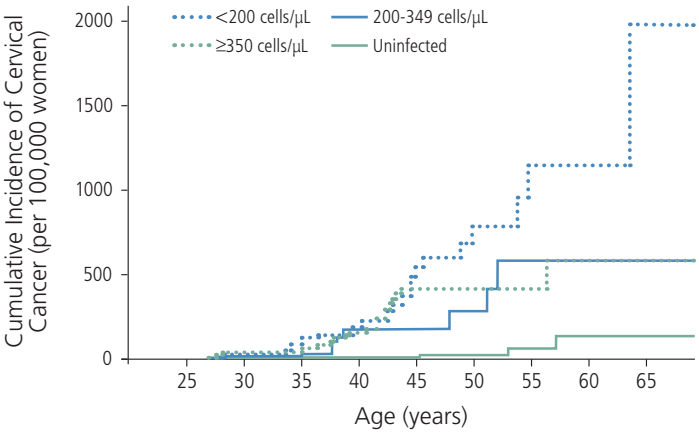

Figure. Risk for invasive cervical cancer according to CD4+ cell count in HIV-infected women. Adapted from Abraham et al.[5]

Cervical Cancer Screening Guidelines

Guidelines for screening for HPV-related cervical disease in HIV-uninfected women include those by the US Preventive Services Task Force (USPSTF)[8]; those endorsed by the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP)[9]; and those by the ASCCP that address the management of abnormal cervical cancer screening tests and cancer precursors.[10] For HIV-infected women, the guidelines most often referred to are those for the prevention and treatment of opportunistic infections (OIs) in HIV-infected adults and adolescents endorsed by the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America.[11] A goal of each of these guidelines is to aid in the prevention of cervical cancer by screening, by evaluation of women with positive test results, and by treatment of biopsy-confirmed high-grade cancer precursors.

General Guidelines

Guidelines for screening of HIV-seronegative and -seropositive women for cervical cancer are compared in the Table.[11,12] For HIV-seronegative women, it is recommended that screening for cervical cancer begin at age 21 years. Young women without HIV infection have a high rate of regression of HPV infection, and intervention with colposcopy or treatment is not generally recommended except in cases of high-grade disease.

However, HIV-infected women have higher rates of HPV infection and cervical intraepithelial neoplasia (CIN) and lower rates of regression of HPV infection. Thus, it is recommended that HIV-infected women who are younger than 21 years and who are sexually active be screened for cervical cancer within 1 year of onset of sexual activity but by no later than age 21 years. HIV-infected women who are aged 21 years to 29 years should have a Pap test performed at the time of initial diagnosis of HIV infection and then annually if the previous Pap test result is normal. If the initial Pap test result shows an abnormality greater than atypical squamous cells of undetermined significance (ASCUS), then colposcopy should be performed; treatment for HIV-infected adolescents should be reserved for CIN of grade 3 or worse. Adult women with ASCUS should have a colposcopy performed immediately or should undergo repeat cytology in 6 months to 12 months. A finding of ASCUS or higher on repeat cytology results should prompt colposcopy. Screening for cervical cancer in HIV-infected women should continue throughout a woman's lifetime and not, as for uninfected women, end at age 65 years. As with HIV-seronegative women, HIV-infected women with a history of high-grade cervical disease or invasive cervical cancer should continue to undergo annual Pap testing after a hysterectomy.

It is currently recommended that HIV-infected women undergo annual screening for cervical cancer, although new data suggest that women with serially negative Pap test results may consider a longer screening interval. A study in the WIHS cohort showed that among 942 HIV-infected women with normal Pap test results at baseline, high-grade CIN developed in 1% within 15 months and in 4% within 39 months.[13] However, among women with normal results on 3 consecutive Pap tests, there were no cases of precancer after 15 months and 2% developed precancer after 39 months. None of the women developed precancer or cancer within 39 months after having normal results on 10 consecutive Pap tests. These findings indicate that a 3-year screening interval may be appropriate for HIV-infected women whose Pap test results are persistently normal and who are adherent to routine care.

Role of Human Papillomavirus DNA Testing

Current USPSTF, ACS, ASCCP, and ASCP recommendations for HIV-seronegative women indicate that a Pap test and HPV DNA test should be performed for women aged 30 years or older and, if the results are normal and negative, respectively, that screening should be performed again in 5 years.[8] HPVDNA testing is appropriate for use in the triage of HIV-uninfected women with ASCUS to determine the need for colposcopy, in the management of postmenopausal women with LSILs, and as follow-up after a colposcopy or treatment procedure (eg, a loop electrosurgical excision procedure or cone biopsy). Current ASCCP guidelines recommend HPV DNA testing to triage ASCUS for HIV-infected and uninfected women. If Pap test results reveal ASCUS and reflex HPV DNA testing results are positive, then a colposcopy is recommended.

In a study in the WIHS cohort, HPV DNA testing was performed when ASCUS was first detected via a Pap test during semiannual follow-up over an 8-year period.[14] Among evaluable cases (successful PCR amplification), HPV test results were positive in 16 of 17 (94%) patients with CIN of grade 2 or worse and in 35 of 97 (36%) patients with CIN of less than grade 2, yielding an overall sensitivity rate of 94% and an overall specificity rate of 64%. These findings suggest that HPV testing to triage ASCUS would detect most cases of CIN

of grade 2 or worse and would allow individuals with CIN of less than grade 2, approximately two-thirds of patients in this study, to avoid colposcopy.

The current CDC/NIH/HIVMA OI guidelines recommend that the ASCCP guidelines be followed for the management of HIV-infected women with abnormal cervical screening test results. With regard to whether Pap and HPV DNA testing can be used to lengthen the screening interval in HIV-infected women with normal Pap test results and negative results on HPV DNA testing, a study in the WIHS cohort reported in 2005 showed a low 5-year risk of cervical precancer and cancer among HIV-seropositive women with normal Pap test results and negative HPV test results.[15] However, this study was based on cytology data, lacked histology data, and included data from before the widespread use of potent antiretroviral therapy.

More recently, the incidence of precancer and cancer was assessed among 420 HIV-infected women and 279 uninfected women in the WIHS population.[16] HIV-infected women with a normal Pap test result and a negative oncogenic HPV test result who were in long-term follow-up had a similar risk of cervical precancer and cancer to uninfected women through at least 5 years of follow-up. The median age was 33 years in the HIV-infected group and 29 years in the uninfected group, and 56% of the HIV-infected women had CD4+ cell counts of 500/μL or greater, 47% were taking antiretroviral therapy, and 88% tested negative for oncogenic HPV DNA. Analysis of outcomes in HIV-infected and uninfected women who had normal Pap test results and negative results on HPV DNA testing showed that HSIL occurred in 1 HIV-infected woman (CD4+ cell count > 500/μL) and 1 uninfected woman. The cumulative incidence of CIN of grade 2 or worse among HIV-infected women was 2% in those with a CD4+ cell count less than 350/μL, 2% in those with a CD4+ cell count of 350/μL to 499/μL, and 6% in those with a CD4+ cell count of 500/μL or greater, compared with 5% in uninfected women. Overall, the 5-year cumulative incidence of CIN of grade 2 or worse was 5% in HIV-infected and uninfected women, and the 5-year cumulative incidence of CIN of grade 3 or worse was 0.5% in HIV-infected women and 0.7% in uninfected women; no cases of cervical cancer were identified. Over 9 years of follow-up, the incidence of CIN of grade 3 or worse was 2% in HIV-infected women and 0.7% in uninfected women, with no cases of cervical cancer identified. These data led the CDC/NIH/HIVMA Panel on OIs in HIV-Infected Adults and Adolescents to recommend cotesting (Pap testing and HPV testing) as an acceptable screening approach for HIV-infected women aged 30 years or older.

Table. Cervical Cancer Screening Guidelines

	USPSTF/ACS/ASCCP/ASCP Guidelines for Women Without HIV Infection	CDC/NIH/HIVMA Guidelines for Women With HIV Infection
Age at initiation of screening	Age 21 y, regardless of risk factors	Within 1 y of onset of sexual activity but by no later than age 21 y
Frequency of screening		
Age 21-29 y	Pap test every 3 y	Pap test every 3 y after 3 consecutive Pap test results are normal
Age ≥30 y	Pap test every 3 y or Pap test and HPV DNA test (cotesting) every 5 y	Pap test every 3 y after 3 consecutive Pap test results are normal, or Pap test and HPV DNA test (cotesting) every 3 y
Discontinuation of screening	Age 65 y	Never
Screening after hysterectomy	Discontinue for benign reasons and no history of CIN of grade 2 or worse for 20 y, otherwise routine screening for at least 20 y	Discontinue for benign reasons and no history of CIN of grade 2 or worse, otherwise annual screening
HPV vaccinated	No change	No change

Abbreviations: ACS, American Cancer Society; ASCCP, American Society for Colposcopy and Cervical Pathology; ASCP, American Society for Clinical Pathology; CDC, Centers for Disease Control and Prevention; CIN, cervical intraepithelial neoplasia; HIVMA, HIV Medicine Association; HPV, human papillomavirus; NIH, National Institutes of Health; Pap, Papanicolaou; USPSTF, US Preventive Services Task Force. Adapted from Moyer[12] and Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents.[11]

Similarly, data from Kaiser Permanente Northern California from 245 HIV-infected women aged 30 years or older, who had normal Pap test results and negative HPV DNA test results, showed no cases of CIN of grade 2 or worse and 1 case of HSIL during 42 months of follow-up.[17] These findings suggest that it may be acceptable to extend cervical cancer screening intervals by performing HPV testing for HIV-infected women who are in routine care, thereby minimizing the potential harms of cytologic screening, including psychological distress (anxiety, concern) related to positive results and risk of adverse effects with additional procedures (colposcopies and biopsies).

Pregnancy

Pregnant women with HIV infection should undergo similar screening to women with HIV infection who are not pregnant. The only finding that would affect the management, timing, and route of delivery of screening is invasive cancer. Pap testing is recommended at the initial prenatal visit unless a normal test result was obtained within the past year. Colposcopy to detect ASCUS or LSILs can be delayed until 6 weeks postpartum, with immediate colposcopy recommended for women with HSILs or atypical glandular cells. Treatment for CIN is not recommended unless invasive disease is expected. HPV vaccination is not recommended during pregnancy, although in 5 trials, vaccination in women who became pregnant did not appear to negatively affect pregnancy outcomes.[18]

Conclusion

Abnormal cervical cytology is common among HIV-infected women. At this time, annual Pap tests are the standard of care. For ASCUS, colposcopy or repeat cytology in 6 months to 12 months is recommended (colposcopy can be deferred until 6 weeks postpartum for pregnant women). Referral for colposcopy should occur if Pap test results reveal ASCUS or worse. There appears to be a role for cotesting for HPV infection to determine screening intervals in HIV-infected women, and a negative result on an oncogenic HPV test has a strong negative predictive value for precancer and cancer, similar to that seen in uninfected women.

The risk of cervical precancer in HIV-infected women with a positive oncogenic HPV test result despite normal cervical cytology is also important for setting screening practices. A recently completed study in the WIHS cohort showed that HIV-infected women with a normal Pap test result who test positive for HPV-16 have a high risk of cervical precancer that may warrant immediate colposcopy, whereas those who test positive for other oncogenic HPV types are at moderate risk that may warrant repeat cotesting in 1 year.[19] Current data suggest that HIV-infected women may benefit from cotesting, as is recommended for the general female population. Future studies should incorporate HPV tests with greater specificity. Examples of molecular assays currently under investigation include the p16/Ki-67 cytology and E6/E7 messenger RNA assays. Currently, there are no national guidelines for routine anal Pap screening in HIV-infected women. At present, many specialists recommend anal cytologic screening, with test results that reveal abnormalities greater than ASCUS prompting a high-resolution anoscopy.

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Special Contribution

HIV-Related Cardiovascular Disease, Statins, and the REPRIEVE Trial

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HIV infection is associated with increased cardiovascular disease (CVD), and increased rates of myocardial infarction and stroke have been observed in HIV-infected individuals. After traditional risk factors that are more common among people living with HIV infection (such as smoking and diabetes) are accounted for, the excess risk for CVD persists. Recent studies suggest that increased immune activation and inflammation may contribute to excess risk for CVD in the context of HIV infection. Imaging studies in the HIV-infected population have found inflamed, noncalcified plaque that is vulnerable to rupture. Statin therapy may represent a potentially useful primary prevention strategy for CVD in HIV-infected individuals, as this class of drugs lowers lipid levels and may simultaneously reduce immune activation and inflammation. REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) is a large, multicenter study funded by the National Institutes of Health. REPRIEVE will test whether pitavastatin, a newer statin that does not have substantial interactions with antiretroviral drugs, can prevent vascular events over time among HIV-infected individuals who do not have known CVD. This study is now open to enrollment at sites throughout the United States and abroad and will hopefully provide definitive data on this important question.

Keywords: HIV, REPRIEVE trial, cardiovascular disease, CVD

Cardiovascular Disease in the HIV-Infected Population

The use of more potent antiretroviral therapy has increased survival among people living with HIV infection. Nonetheless, even as the prevalence of opportunistic infections is declining, the prevalence of non–AIDS-related comorbidities, including cardiovascular disease (CVD), remains increased among HIV-infected individuals compared with uninfected individuals.[1] A consistent body of evidence demonstrates that people living with HIV infection are 50% to 100% more likely to develop CVD than people without HIV infection, even when additional risk factors are controlled for, such as hypertension, cholesterol, and smoking status.[2] Most recently, data on 82,459 patients in the Veterans Aging Cohort Study found that patients with HIV infection had a 1.5-times higher risk of acute myocardial infarction than the general population.[3]

Imaging studies have shed light on the mechanisms of CVD in HIV-infected individuals. Findings from initial studies that used computed tomography (CT) angiography suggested an increased prevalence of coronary plaque in almost 60% of HIV-infected participants compared with 30% of an uninfected control group who had similar traditional risk factors. Moreover, lesions were more often noncalcified and had more high-risk morphologic features, including low attenuation and positive remodeling, 2 features that suggest high-risk plaque that is vulnerable to rupture.[4,5] In studies that used ^{18}fluorine-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG-PET) imaging, increased arterial inflammation was observed among HIV-infected individuals matched for traditional coronary risk factors.[6] Taken together, these studies suggest a unique morphology of high-risk inflamed plaque among HIV-infected individuals. Of note, subclinical CVD may occur among HIV-infected individuals with low or moderate traditional risk who may not be well identified by conventional risk scoring.[7] Indeed, high-risk plaque is substantially associated with increased immune activation, more so than other risk factors, suggesting that immune activation and inflammation may contribute to the unique pathophysiology of CVD in HIV-infected individuals.

Development of a successful primary prevention strategy is crucial for the HIV-infected population. In this regard, a number of different strategies may be useful to prevent CVD in HIV-infected individuals. In the SMART (Strategies for Management of Antiretroviral Therapy) study, consistent use of antiretroviral therapy in individuals with CD4+ cell counts below 350/μL resulted in a decrease in AIDS-related adverse events and in CVD events.[8] In the START (Strategic Timing of Antiretroviral Treatment) study, although AIDS-related events were reduced, utilization of early, CD4+ cell count–guided antiretroviral therapy did not reduce CVD events. However, relatively few CVD events were observed among antiretroviral therapy–naive individuals who may have had somewhat shorter durations of HIV infection.[9] Taken together, these data suggest that suppressive antiretroviral therapy based on stricter CD4+ cell count thresholds will likely result in decreased rather than increased CVD rates, particularly as newer antiretroviral regimens with fewer metabolic effects are utilized. However, CVD rates currently remain increased

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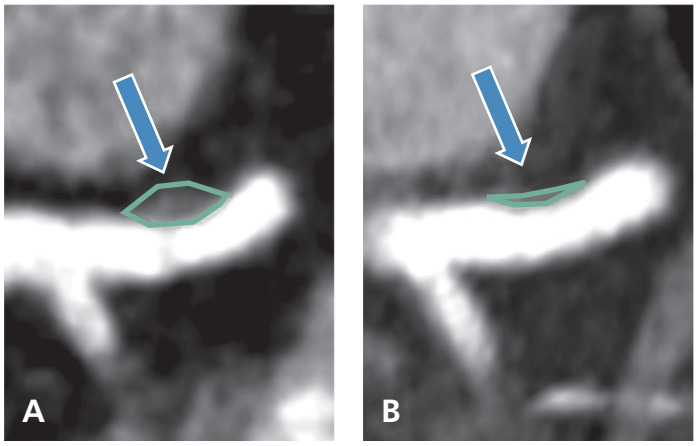

Figure 1. Noncalcified plaque in the proximal left anterior descending coronary artery in an individual before (A) and after (B) 12 months of therapy with atorvastatin.

among HIV-infected individuals, even those taking antiretroviral therapy who are virally suppressed, suggesting that other strategies are needed.

Lifestyle modification and treatment of traditional risk factors, including those for hypertension and diabetes, are important initial strategies. In addition, smoking cessation will prevent heart disease and is an important strategy in the large group of HIV-infected individuals who continue to smoke. However, a key question is whether these strategies targeting individual traditional risk factors are sufficient? The answer remains unknown, but it is interesting to speculate that other strategies may be needed, as the risk of hypertension and diabetes, although increased among HIV-infected individuals, does not fully account for the marked increase in CVD in this population.[1] Moreover, substantial data have emerged that suggest that excess CVD risk is associated with immune activation among HIV-infected individuals.

Statins

Statins may be particularly useful in the HIV-infected population, as they have the advantage of lowering low-density lipoprotein (LDL) cholesterol, a known traditional CVD risk marker, and of reducing immune activation and inflammation. Statins have been shown to consistently lower mortality rates among HIV-uninfected individuals in association with reductions in LDL cholesterol levels.[10] The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial included uninfected participants without known CVD and with reasonably controlled LDL cholesterol levels (< 130 mg/dL). Participants in the JUPITER trial were required to have evidence of inflammation, as documented by increased C-reactive protein. In JUPITER, rosuvastatin use was shown to reduce future CVD events by 44%, more than would be expected by lowering of LDL cholesterol level alone.[11]

Among HIV-infected individuals, initial studies have begun to assess the potential utility of statin therapy. The general safety and efficacy of statins on liver, muscle, and LDL cholesterol were examined in a large cohort study by Silverberg and colleagues.[12] In the study, statin use reduced LDL cholesterol levels by 26% and resulted in a 2% or lower prevalence of substantial muscle or liver adverse effects.

Funderberg and colleagues demonstrated the effects of rosuvastatin on improving key indices of immune activation among HIV-infected individuals, including indices of monocyte (soluble CD14, $CD14^{dim}$CD16+TF+ subsets) and T-cell (CD4+CD38+HLA-DR+) activation.[13] In addition, preliminary double-blind, placebo-controlled trials suggest that statins may improve high-risk plaque morphology in HIV-infected individuals by reducing noncalcified plaque volume, high-risk coronary plaque features, and markers of vascular inflammation (Figure 1).[14]

Despite the emerging data on statin efficacy in HIV-infected individuals, key questions must be answered before this class of drugs can be recommended as a prevention strategy for CVD in the context of HIV infection. The small initial studies performed to date among HIV-infected participants have not yet investigated the effects of statins on actual CVD events but rather on plaque indices and inflammatory markers. Thus, it remains to be established if the robust effects seen on plaque in the context of HIV infection will translate to a reduction in CVD events. In addition, safety and tolerability concerns must be fully addressed. Some statins (eg, simvastatin and, to a lesser extent, atorvastatin) may interact with protease inhibitors through metabolic pathways involving cytochrome P450 3A.[15] Some newer statins, including pitavastatin, are glucuronidated and are not known to interact with currently available antiretroviral drugs. Whereas some studies have suggested that certain statins increase glucose level, pitavastatin was not shown to have an adverse effect on diabetes or glucose level in the large, recently completed INTREPID (HIV-Infected Patients and Treatment With Pitavastatin vs Pravastatin for Dyslipidemia) study conducted among HIV-infected individuals.[16]

The REPRIEVE Trial

Given the crucial need for prevention of CVD events among HIV-infected individuals and the encouraging data to date on statins in this population, the National Institutes of Health (NIH) recently launched a large trial to definitively assess the efficacy of statins as a primary prevention strategy for CVD in this at-risk population. The REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial was launched in April 2015 and is the largest clinical trial of HIV-related CVD to date. The REPRIEVE trial will enroll 6500 HIV-infected participants who have no known clinical history or symptoms of CVD. Participants will be randomly assigned to receive daily pitavastatin 4 mg or a placebo for an average of 4 years (Figure 2), depending on date of entry into the trial. The trial is being conducted in collaboration with 100 plus sites from the AIDS Clinical Trials Group (ACTG) network and other NIH Division of AIDS networks in the United States and internationally, including sites in Canada, Thailand, and Brazil.

REPRIEVE is a collaborative study funded primarily by the NIH National Heart, Lung, and Blood Institute with additional support from the National Institute of Allergy and Infectious Diseases. In addition, the NIH Office of AIDS Research has contributed substantially to the project by providing additional funding. Reflecting the multidisciplinary nature of the REPRIEVE trial, the core team of researchers consists of specialists in metabolic aspects of HIV disease, cardiology, radiology, and AIDS care. The drug, pitavastatin, along with some additional funding is being donated to the trial by the manufacturer (Kowa Pharmaceuticals, Montgomery, AL). Pitavastatin was selected for REPRIEVE because it has had fewer interactions with antiretroviral drugs than other statins and effectively lowers LDL cholesterol levels in people living with HIV infection.[17]

Trial Design

The REPRIEVE trial will investigate the crucial question of whether HIV-infected individuals with low or moderate risk of heart disease, estimated using traditional risk assessment paradigms,[18] will benefit from statin therapy. To be enrolled in the trial, participants must be between age 40 years and 75 years, taking an antiretroviral regimen, have no known CVD or substantial kidney or liver disease, and have a CD4+ cell count higher than 100/μL (Box). There is no specific viral load cut off for the trial, although it is anticipated that most patients taking antiretroviral therapy will demonstrate undetectable viremia (see www.REPRIEVEtrial.org for inclusion criteria, participating sites, and other information). The primary end point of REPRIEVE will be prevention of major adverse cardiovascular events, including CVD-related mortality, myocardial infarction, stroke, unstable angina, peripheral artery disease, and cardiac revascularization. The REPRIEVE trial will also investigate the effects of statin therapy on secondary outcomes, such as all-cause mortality, time to diagnosis of non–AIDS-defining cancer (excluding basal cell and squamous cell carcinomas of the skin), AIDS-defining events, initiation of dialysis or renal transplantation, cirrhosis, or hepatic decompensation requiring hospitalization. It is hypothesized that by decreasing inflammation and immune activation, statins may improve these related comorbidities.

In addition to the main study, REPRIEVE will include a substudy of 800 participants to investigate the mechanism of action of pitavastatin, particularly in reducing immune activation and inflammation. Biomarkers will be investigated and cardiac CT angiography will be performed to assess the effect of pitavastatin on noncalcified plaque volume and high-risk arterial morphologic features in the context of a large, randomized, placebo-controlled trial. Effects on specific biomarkers of monocyte activation, endothelial activation, arterial inflammation, and coagulation will be investigated and related to the primary study outcomes. Two ancillary studies have also been funded by the NIH: 1) to evaluate the longitudinal effects of statin therapy on renal function in HIV disease; and 2) to explore sex-specific mechanisms of CVD risk and statin-induced risk reduction among participants in the REPRIEVE trial.

Current Status

The REPRIEVE trial was launched in April 2015, with its first participant recruited approximately 6 months after the grant was awarded, a major triumph given the complex regulatory hurdles associated with launching a trial of this magnitude. As of November 2015, approximately 600 patients are enrolled in REPRIEVE. Continued recruitment efforts are needed in order to meet the NIH-mandated goal of completing recruitment within the first 2.5 years of the trial. Participants in the main trial will visit their local site once every 4 months for the duration of the study. Participants in the substudy will also have blood drawn to assess biomarkers and undergo CT angiography at baseline and at 2 years.

Goals

The REPRIEVE trial represents a new paradigm in studies of comorbidities in HIV-infected individuals. As HIV-infected individuals are living longer with fewer AIDS-related complications, understanding the mechanism and treatment strategies for prevention of comorbidities becomes increasingly important. Unlike prior shorter-term studies that assessed biomarkers, the REPRIEVE trial will assess effects on hard end points. Therefore, data will need to be captured over a longer time period. Without such studies, whether primary prevention strategies save lives in the HIV-infected population will remain unknown. The REPRIEVE trial was designed to be a simple study with straightforward clinical assessments using participant histories and minimal blood work. Importantly, REPRIEVE will provide information to all enrolled participants on lifestyle modifications to improve CVD risk. Clinical equipoise remains regarding the ability of

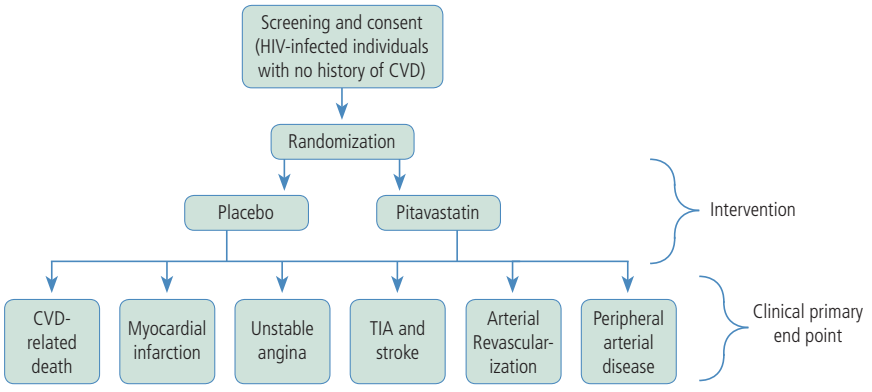

Figure 2. Schema of the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) study in which participants will be randomly assigned to receive daily pitavastatin 4 mg or a placebo for an average of 4 years. CVD indicates cardiovascular disease; MI, myocardial infarction; TIA, transient ischemic attack.

Box. Eligibility Criteria for Participants in the REPRIEVE Trial

- Must have HIV infection
- Must be between age 40 years and 75 years
- Must have been taking antiretroviral therapy for at least 6 months
- Must have a CD4+ cell count greater than 100/µL
- Must have no history of cardiovascular disease (eg, heart attack or stroke)
- Must not be currently taking a statin
- Must have low or moderate risk of cardiovascular disease according to the 2013 American College of Cardiology/American Heart Association risk calculator (http://www.cvriskcalculator.com)

Abbreviations: REPRIEVE, Randomized Trial to Prevent Vascular Events in HIV.

long-term statin use to prevent HIV-related CVD, and many clinicians are waiting for results from the REPRIEVE trial to inform their practice. As the HIV-seropositive population ages, now is a crucial time to study this relationship.

Summary

Tailored strategies to prevent heart disease are urgently needed in the HIV-infected population in whom the risk of CVD remains increased even as rates of traditional AIDS-related morbidities decrease. The NIH has recognized this important gap in knowledge of HIV disease. On a larger scale, the REPRIEVE trial has the potential to advance understanding of how inflammation should be incorporated into CVD risk prediction analyses, which are not generally accounted for in these measures. Results from the REPRIEVE trial may also provide important insights into other inflammatory conditions in which increased CVD rates are seen. Results from the REPRIEVE trial should become available in the next 5 years to 6 years and may influence future US guidelines for lowering the risk of heart-related disease among an aging HIV-infected population that is subject to an increasing prevalence of comorbidities related to chronic inflammation.

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