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Perspective

HIV Treatment and Prevention: An Overview of Recommendations From the 2016 IAS–USA Antiretroviral Guidelines Panel

Updated recommendations from the IAS–USA Antiretroviral Guidelines Panel on antiretroviral therapy for the treatment and prevention of HIV infection in adults were published in the Journal of the American Medical Association *in 2016. The updated, evidence-based recommendations address when to initiate antiretroviral therapy, recommended initial antiretroviral regimens, including integrase strand transfer inhibitor (InSTI)-based regimens, recommended regimens for persons in whom an InSTI is not an option, and special treatment considerations. The interface between antiretroviral therapy and opportunistic infections, when and how to switch antiretroviral therapy, laboratory monitoring, engagement in care, adherence to antiretroviral therapy, and use of antiretroviral therapy as HIV prevention are also discussed, as well as future directions in HIV treatment. This article summarizes an IAS–USA continuing education webinar presented by Paul A. Volberding, MD, in August 2016.*

Keywords: HIV, antiretroviral therapy, recommendations, initial antiretroviral regimens, opportunistic infections, switching antiretroviral therapy, prevention

Updated recommendations from the IAS–USA Antiretroviral Guidelines Panel on antiretroviral therapy for the treatment and prevention of HIV infection in adults were published in the *Journal of the American Medical Association* in 2016.[1] The recommendations were updated based on data supporting that all HIV-infected persons should receive antiretroviral therapy regardless of CD4+ cell count, new data on antiretroviral approaches for the treatment and prevention of HIV infection, and data on investigational uses of antiretroviral drugs. The 2016 recommendations include updated options for initial antiretroviral therapy, guidance for switching antiretroviral treatment in persons who achieve virologic suppression, recommendations for improving retention in care and adherence to treatment, and discussion of future directions in HIV treatment and prevention. Table 1 provides the rating system for the strength of the recommendations and the quality of evidence supporting these recommendations. The full text of the article is available at no charge at www.jamanetwork.com.

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When to Initiate Antiretroviral Therapy

Recommendations regarding when to initiate antiretroviral therapy are shown in Box 1. Initiation of antiretroviral therapy is recommended for all HIV-infected persons with detectable viremia, regardless of CD4+ cell count; persons with acute HIV infection in whom antiretroviral therapy should be initiated as soon as possible; and persons who have persistently undetectable viral loads without antiretroviral therapy ("elite controllers") but who have declining CD4+ cell counts.

Planned discontinuation of early antiretroviral therapy after a specific duration of treatment is not recommended outside of a research setting. There is renewed interest in cure research using analytic treatment interruptions. However, planned discontinuation of antiretroviral treatment should only occur in the setting of a research trial in which individuals are closely monitored for viral relapse and promptly retreated.

Recommended Initial Antiretroviral Regimens

The recommended initial antiretroviral treatment is an integrase strand transfer inhibitor (InSTI) plus 2 nucleos(t)ide analogue reverse transcriptase inhibitors (nRTIs). InSTIs may

Table 1. Ratings for Strength of Recommendation and Quality of Evidence

Rating	Definition
Strength of recommendation	
A	Strong support for the recommendation
B	Moderate support for the recommendation
C	Limited support for the recommendation
Quality of evidence	
Ia	Evidence from 1 or more randomized clinical trials published in the peer-reviewed literature
Ib	Evidence from 1 or more randomized clinical trials presented in abstract form at peer-reviewed scientific meetings
IIa	Evidence from nonrandomized clinical trials or cohort or case-control studies published in the peer-reviewed literature
IIb	Evidence from nonrandomized clinical trials or cohort or case-control studies presented in abstract form at peer-reviewed scientific meetings
III	Recommendation based on the panel's analysis of the accumulated available evidence

Adapted in part from Canadian Task Force on Periodic Health Examination.[9]

Table 2. Recommended Initial InSTI-Containing Regimens[a]

InSTI-Containing Regimens	Evidence Rating	Advantages of InSTI	Disadvantages of InSTI
Dolutegravir: Dolutegravir/abacavir/lamivudine Dolutegravir plus TAF/emtricitabine or TDF/emtricitabine	AIa	Superior to efavirenz and ritonavir-boosted darunavir in comparative clinical trials Once-daily dosing Dolutegravir (not coformulated) pill size is small Lowest risk of resistance with virologic failure Relatively few drug interactions Can be taken with or without food Superior to raltegravir in treatment-experienced persons	Only available coformulation is with abacavir/lamivudine Raises serum creatinine level owing to inhibition of tubular secretion of creatinine Higher rates of insomnia and headache than comparators in some studies Largest tablet among coformulated single-pill regimens
Elvitegravir: Elvitegravir/cobicistat/TAF (or TDF)/emtricitabine	AIa	Superior to ritonavir-boosted atazanavir in comparative clinical trial of HIV-infected women Once-daily dosing	Requires pharmacokinetic boosting with cobicistat or ritonavir for once-daily dosing Most drug interactions Cobicistat raises serum creatinine level owing to inhibition of tubular secretion of creatinine Should be taken with food
Raltegravir: Raltegravir plus TAF/emtricitabine	AIII	Superior to ritonavir-boosted atazanavir and ritonavir-boosted darunavir in a comparative clinical trial Longest safety record Fewest drug interactions Can be taken with or without food	Currently must be taken twice daily Not coformulated as part of a complete regimen[b]

Abbreviations: InSTI, integrase strand transfer inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from Günthard et al.[1]

[a]Slashes indicate a coformulation.

[b]Formulation consisting of 2 pills given once daily is in development.

be unavailable in some resource-limited settings; however, they are likely to become more available in the near future.

The 3 main currently available InSTIs are dolutegravir, elvitegravir, and raltegravir, and other InSTIs are in development (Table 2). Data on these InSTIs vary (eg, prospective data on the use of raltegravir and tenofovir alafenamide [TAF] are limited). InSTIs have a lower risk for drug-drug interactions than other classes of antiretroviral drugs. Of note, dolutegravir is associated with low risk for resistance with virologic failure compared with the other 2 drugs in this class without the need for boosting, which is required for elvitegravir. In sum, current data support the use of InSTIs as part of initial antiretroviral therapy.

Box 1. Recommendations for When to Initiate Antiretroviral Therapy

Initiation of antiretroviral therapy is recommended for[a]:

- All HIV-infected persons with detectable viremia, regardless of CD4+ cell count (AIa)
- Persons with acute HIV infection. Antiretroviral therapy should be initiated as soon as possible (BIII)
- Persons with persistent undetectable viral load without antiretroviral therapy ("elite controllers") but who have declining CD4+ cell counts (BIII)

Planned discontinuation of early antiretroviral therapy after a specific duration of treatment is not recommended outside of a research setting (AIa)

Adapted from Günthard et al.[1]

[a]Baseline resistance testing is recommended for all persons, but initiating therapy prior to availability of the results may be appropriate in some cases.

Recommended non–InSTI-containing initial antiretroviral regimens are darunavir (boosted with cobicistat or ritonavir) plus TAF/emtricitabine (slash indicates a coformulation), tenofovir disoproxil fumarate (TDF)/emtricitabine, or abacavir/lamivudine; efavirenz/TDF/emtricitabine; or rilpivirine plus TAF/emtricitabine or TDF/emtricitabine. It is likely that many HIV-infected individuals are taking these regimens at present. Advantages and disadvantages of these regimens are shown in Table 3.

Table 4 shows recommended initial regimens in the setting of special considerations: pregnancy, HIV/hepatitis B virus (HBV) coinfection, HIV/hepatitis C virus (HCV) coinfection, osteopenia or osteoporosis, and kidney disease. Some treatment recommendations for HIV-infected pregnant women, such as that for use of the InSTI raltegravir, reflect more clinical experience. TDF, TAF, lamivudine, or emtricitabine, which have activity against HBV infection, should not be discontinued

Table 3. Recommended Initial Non–InSTI-Containing Regimens[a]

Non–InSTI-Containing Regimens	Evidence Rating	Advantages	Disadvantages
Darunavir/cobicistat or darunavir/ritonavir plus TAF/emtricitabine, TDF/emtricitabine, or abacavir/lamivudine	AIa	Low risk of resistance with virologic failure, even with intermittent adherence	Requires pharmacokinetic boosting; many drug interactions Ritonavir-boosted darunavir inferior to raltegravir and dolutegravir in separate comparative clinical trials Results of comparative, fully powered studies of cobicistat-boosted darunavir as initial therapy are not yet available
Efavirenz/TDF/emtricitabine	AIa	High efficacy in individuals with baseline HIV RNA level >100,000 copies/mL Extensive experience in individuals with concomitant tuberculosis Widely available globally	Relatively high rate of rash No single-tablet form available with TAF High rates of neuropsychiatric adverse effects Increased risk of suicidality in one study; avoid in patients with history of depression
Rilpivirine/TAF (or TDF)/emtricitabine	AIa	Lowest risk of rash among NNRTI-based therapies Low risk of metabolic adverse effects Smallest tablet among single-pill regimens	Not recommended for patients with HIV RNA level >100,000 copies/mL or CD4+ cell count <200/μL owing to increased risk of virologic failure Must be taken with a meal Should not be administered with proton pump inhibitors; stagger dosing if given with an H_2 blocker

Abbreviations: InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from Günthard et al.[1]

[a]Slashes indicate a coformulation.

in HIV/HBV-coinfected persons. Entecavir may be considered as a treatment option for HIV/HBV-coinfected persons, although it can select for lamivudine- and emtricitabine-resistant HIV and should not be used if virus is not suppressed. The recommendations list the antiretroviral drugs that have the fewest interactions with current HCV direct-acting antiviral drugs. However, the field of HCV treatment is changing rapidly, with regular introduction of new HCV drugs, and HCV treatment guidelines should be consulted frequently for updated information.[2]

Other special considerations include treatment for HIV-infected persons with known osteopenia or osteoporosis. TDF should be avoided in the setting of osteopenia or osteoporosis; there is evolving evidence that other nRTIs, including abacavir and TAF, may be used instead. Kidney disease also poses a challenge due to renal adverse effects associated with some antiretroviral treatments. The recommendations discuss various options for antiretroviral treatment depending on the degree of underlying renal impairment.

Interface Between Antiretroviral Therapy and Opportunistic Infections

Discussion of the interface between antiretroviral therapy and opportunistic infections (OIs) is important because OIs are far less common in many settings and warrant the revisiting of treatment principles, and because they remain common in some resource-limited settings. Recommendations

Box 2. Recommendations for the Interface Between Antiretroviral Therapy and Opportunistic Infections

- Initiate antiretroviral therapy within the first 2 weeks after diagnosis for most acute opportunistic infections, with possible exception of acute cryptococcal meningitis (AIa)
- Initiate antiretroviral therapy within the first 2 weeks of initiation of tuberculosis treatment for persons with CD4+ cell counts of 50/μL and within the first 2 to 8 weeks for those with CD4+ cell counts above 50/μL (AIa)
- Avoid using TAF or cobicistat-boosted elvitegravir with rifamycins (AIIb)
- Boosted protease inhibitor (PI)-based regimens should only be used if an InSTI is not an option, and rifabutin 150 mg daily should be substituted for rifampin in the anti-TB regimen (AIa)
- Primary MAC prophylaxis is not recommenced if effective antiretroviral therapy is initiated immediately (AIIa)
- Primary PCP prophylaxis is still recommended for those who meet CD4+ cell count criteria (AIa)

Abbreviations: MAC, *Mycobacterium avium* complex; PCP, *Pneumocystis jiroveci* pneumonia; PI, protease inhibitor; TB, tuberculosis. Adapted from Günthard et al.[1]

Table 4. Recommended Initial Antiretroviral Regimens: Special Considerations[a]

Special Consideration	Evidence Rating	Advantages	Disadvantages
Pregnancy	AIa	Abacavir/lamivudine (if HLA-B*5701 negative), TDF/emtricitabine, or zidovudine/lamivudine Raltegravir is the recommended InSTI Recommended boosted PIs include atazanavir/ritonavir (once daily) or darunavir/ritonavir (twice daily) Efavirenz is the recommended NNRTI when initiated after the first 8 weeks of pregnancy	Initiate antiretroviral therapy for the woman's own health and to reduce likelihood of mother-to-child transmission of HIV (AIa)
HBV coinfection	AIa	Initiate recommended antiretroviral therapy regimen that contain TDF or TAF, lamivudine or emtricitabine, and a third component	High risk of HBV resistance and viral breakthrough if lamivudine or emtricitabine are used without TDF or TAF, and neither is recommended alone for HBV coinfection
	AIII	Entecavir may be used but should be avoided if HIV RNA is not suppressed	Entecavir may be used but should be avoided if HIV RNA is not suppressed
HCV coinfection	AIIa	Regimens that have the fewest drug interactions with current HCV treatments are: • dolutegravir/abacavir/lamivudine • dolutegravir or raltegravir plus TAF/emtricitabine	Avoid antiretroviral drugs with substantial drug interactions with HCV therapies Clinicians should consult current HCV treatment guidelines prior to using any other antiretroviral therapy regimens, particularly those that include NNRTIs, boosted HIV PIs, or elvitegravir/cobicistat
Osteopenia or osteoporosis	AIa	Dolutegravir/abacavir/lamivudine	TDF is not recommended (BIII)
	AIa	Dolutegravir plus TAF/emtricitabine	
	AIa	Elvitegravir/cobicistat/TAF/emtricitabine	
	AIII	Raltegravir plus TAF/emtricitabine	
Kidney disease[b]	AIa	Dolutegravir/abacavir/lamivudine	Estimated glomerular filtration rate, urinalysis, and testing for glycosuria and albuminuria or proteinuria when antiretroviral therapy is initiated or changed and every 6 months (BIII) TDF should be avoided in persons with creatinine clearance rate below 60 mL/min (AIa) TDF or TAF should be discontinued if renal function worsens, particularly if there is evidence of proximal tubular dysfunction (AIIa) Persons with end-stage renal disease should be evaluated for kidney transplantation with expectation of high rates of patient and graft survival (AIIa)
	AIa	Dolutegravir plus TAF/emtricitabine	
	AIa	Elvitegravir/cobicistat/TAF/emtricitabine	
	AIII	Raltegravir plus TAF/emtricitabine	
	AIa	TAF can be used if creatinine clearance is above 30 mL/min	
	AIIa	TAF should be initiated only after tubulopathy has resolved, with monitoring for recurrence	

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from Günthard et al.[1]

[a]Slashes indicate a coformulation.

[b]Long-term data on TAF in individuals with renal disease are limited and safety has not been determined.

regarding the interface between antiretroviral therapy and OIs are shown in Box 2.

Antiretroviral therapy should be initiated within 2 weeks of diagnosis for most acute OIs. A possible exception is acute cryptococcal meningitis, as initiating HIV treatment too soon in this setting may result in immune reconstitution inflammatory syndrome, which can cause considerable challenges given the compressed space of the central nervous system. Although there has been much debate, it is recommended that antiretroviral therapy be initiated within the first 2 weeks of initiating tuberculosis (TB) treatment for HIV-infected persons with CD4+ cell counts below 50/μL and

Box 3. Recommendations for When and How to Switch Antiretroviral Therapy

- Induction maintenance strategies are not recommended at this time (BIIa)
- Review of treatment history and results of prior resistance tests is recommended before any treatment switches are made (AIa)
  - Proviral DNA genotype testing may be helpful in detecting archived mutations; however, clinical utility is not yet established and proviral DNA genotype testing may fail to detect existing mutations
- If there is no increase in price, switching from TDF to TAF is reasonable even if patients are not experiencing TDF-related toxic effects (BIa)
- Switching from a boosted PI to an NNRTI or InSTI (with the possible exception of dolutegravir) or switching from twice-daily ritonavir-boosted darunavir to once-daily cobicistat-boosted darunavir is not recommended without consideration of a patient's viral resistance profile (AIII)

Abbreviations: InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from Günthard et al.[1]

within the first 2 to 8 weeks for those with CD4+ cell counts above 50/µL. TAF or cobicistat-boosted elvitegravir should not be used with rifamycins. Further, a boosted protease inhibitor (PI)-based regimen should be used only if InSTIs are not an option, and rifabutin should be substituted for rifampin in TB regimens.

With regard to OI prophylaxis, there is strong evidence that initiating antiretroviral therapy will prevent the need for Mycobacterium avium complex prophylaxis. However, *Pneumocystis jiroveci* pneumonia prophylaxis should still be initiated in persons with a CD4+ cell count below 200/µL.

When and How to Switch Antiretroviral Therapy

Reasons for switching antiretroviral therapy include adverse effects, simplification of regimen (doses or pills), drug-drug interactions, pregnancy or plans for pregnancy, food restrictions, and regimen modernization. Recommendations regarding switching antiretroviral therapy are shown in Box 3.

Review of treatment history and results from prior resistance testing are recommended before any treatment switches are made. Proviral DNA genotype testing may be helpful in detecting archived resistance mutations, to minimize the risk of loss of virologic suppression when switching treatment. However, the clinical utility of proviral DNA genotype testing is not yet established, and it may fail to detect existing resistance mutations.

In the absence of a price increase, modernizing an antiretroviral regimen by switching from TDF to TAF is reasonable to avoid risk of TDF-induced renal and bone toxicities. Switching from a boosted PI to a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) or an InSTI (with the possible exception of dolutegravir) or switching from twice-daily ritonavir-boosted darunavir to once-daily cobicistat-boosted darunavir is recommended, but these switches should not be made without consideration of a person's viral resistance profile.

Laboratory Monitoring

Recommendations for laboratory monitoring reflect evidence that supports specific monitoring practices, although some recommendations for monitoring are based on less than optimal amounts of prospective clinical evidence. Recommendations for laboratory monitoring and a panel of tests that are recommended before initiation of antiretroviral therapy are shown in Box 4. As rapid initiation of antiretroviral therapy becomes more common, including in the setting of acute HIV infection, the necessity of performing these tests before initiation of antiretroviral therapy should be further considered. Genotypic testing for nRTI-, NNRTI-, and PI-associated resistance mutations is recommended for all HIV-infected persons. At this time, routine baseline genotype testing for InSTI-associated resistance mutations is not considered necessary. The rate of InSTI-associated resistance in transmitted virus remains low but warrants monitoring..

All laboratory specimens should be drawn prior to initiation of antiretroviral therapy, and resistance testing results should be used to modify a regimen as necessary. It is recommended that plasma HIV RNA level be monitored every 4 to 6 weeks after initiating or changing antiretroviral therapy until virus is undetectable.

Plasma HIV RNA level should be monitored every 3 months after viral suppression is achieved and until virus is suppressed for 1 year and at least every 6 months thereafter in persons who remain clinically stable. Individuals should be reassessed every 3 to 4 months if their pretreatment CD4+ cell count is below 200/µL until their viral load is reliably suppressed and CD4+ cell count is above 350/µL for 1 year. Thereafter, CD4+ cell count can be assessed at 6-month intervals until virus has been suppressed for at least 2 years and CD4+ cell count is stably above 500/µL.

Measurement of plasma HIV RNA level should be repeated within 4 weeks if it remains above the limit of quantification by 24 weeks after starting new treatment or if there is viral rebound above 50 copies/mL. Tropism testing should be performed at the time of virologic failure of a CC chemokine receptor 5 inhibitor (eg, maraviroc).

Repeat monitoring of CD4+ cell count is not necessary when virus has been suppressed for at least 2 years and CD4+ cell count is persistently above 500/µL, unless virologic failure or intercurrent immunosuppressive conditions occur or immunosuppressive treatment is initiated. However, improved quality of evidence is desired in support of this recommendation.

Box 4. Recommendations for Laboratory Monitoring

Recommended:

- Preantiretroviral therapy tests: CD4+ cell count, plasma HIV-1 RNA, HAV, HBV, and HCV serologies, serum chemistries, estimated creatinine clearance rate, complete blood cell count, urine glucose and protein tests, STI screening, and fasting lipid profile (AIII)
- Genotypic testing for reverse transcriptase and protease mutations for all persons (AIIa)
- Confirmation of HLA-B*5701 and CC chemokine receptor 5 tropism test results prior to initiating therapy with abacavir and maraviroc, respectively
- Draw all laboratory specimens prior to first dose of antiretroviral therapy if antiretroviral therapy is initiated on the first clinic visit (AIII)[a]
- Monitor HIV RNA level every 4 to 6 weeks after initiating or changing treatment until virus is undetectable (AIa)
- Monitor HIV RNA level every 3 months after viral suppression is achieved and until virus is suppressed for 1 year and at least every 6 months thereafter in adherent persons who remain clinically stable (AIII)
- Reassess every 3 to 4 months if pretreatment CD4+ cell count is below 200/μL, and every 3 to 4 months until viral load is reliably suppressed and CD4+ cell count is above 350/μL for 1 year; thereafter, assess CD4+ cell count at 6-month intervals until virus has been suppressed for at least 2 years and CD4+ cell count is stable above 500/μL (AIII)
- Repeat assay within 4 weeks if HIV RNA level remains above the limit of quantification by 24 weeks after initiating new treatment or if rebound above 50 copies/mL occurs (AIIa)
- Tropism testing at the time of virologic failure of a CC chemokine receptor 5 inhibitor (AIa)

Not recommended:

- Routine screening for integrase resistance prior to treatment initiation unless the source virus is suspected to have been from someone in whom treatment containing an InSTI failed (BIII)
- Therapeutic drug monitoring except in specific circumstances (BIII)
- When virus has been suppressed for at least 2 years and CD4+ cell count is persistently above 500/μL, repeat monitoring of CD4+ cell count is not recommended unless virologic failure (AIIa) or intercurrent immunosuppressive conditions occur or immunosuppressive treatments are initiated (AIII)

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; InSTI, integrase strand transfer inhibitor; STI, sexually transmitted infection. Adapted from Günthard et al.[1]

[a]Resistance testing results should be used to modify the regimen as necessary.

Engagement in Care and Adherence to Antiretroviral Therapy

Recommendations regarding engagement in care and adherence to antiretroviral therapy are shown in Box 5. These recommendations are designed to improve early diagnosis of HIV infection, access and linkage to care, retention in care, and adherence to antiretroviral therapy.

Routine opt-out HIV screening is recommended in primary medical care settings and emergency departments and for all pregnant women. Programmatic monitoring of time to care linkage following initial HIV diagnosis, of retention in care, of adherence to antiretroviral therapy, and of rates of viral suppression in all care settings is recommended to collect more and better data on the cascade of HIV care. Emerging evidence supports the role of brief case management after HIV diagnosis in improving engagement in care.[3,4] Similarly, there is evidence that rapid intervention following a missed clinic visit can improve retention in care.[5,6] Additional recommendations have been made for the use of directly observed antiretroviral therapy in methadone maintenance programs and other settings, opioid substitution therapy for opioid-dependent persons, validated adherence instruments for self-reporting and pharmacy refill data to monitor adherence to antiretroviral therapy, and routine screening for depression.

Box 5. Recommendations for Engagement in Care and Adherence to Antiretroviral Therapy

Recommended:

- Routine opt-out HIV screening in primary medical care settings and emergency departments and for all pregnant women (AIII)
- Programmatic monitoring of time to care linkage following initial HIV diagnosis, retention in care, adherence to antiretroviral therapy, and rates of viral suppression in all care settings (AIIa)
- Brief case management after HIV diagnosis (AIa)
- Rapid intervention following a missed clinic visit (AIIa)
- Integration of directly observed antiretroviral therapy in methadone maintenance programs (BIa) and as a treatment strategy among persons with substance use disorders (BIa) and those who are incarcerated or released to the community (CIII)
- Opioid substitution therapy for opioid-dependent persons (AIIa)
- Monitoring of adherence using self-reports by validated adherence instruments and pharmacy refill data (AIIa)
- Routine screening for depression (AIII)

Adapted from Günthard et al.[1]

HIV Prevention

The use of antiretroviral drugs has expanded beyond treatment of HIV infection at an individual level to include treatment as prevention (by reducing transmission risk), preexposure prophylaxis (PrEP), and postexposure prophylaxis (PEP). Recommendations for HIV prevention are shown in Box 6.

PrEP is recommended for populations in which incidences of HIV infection are high and for HIV-uninfected partners of HIV-infected persons who are not virally suppressed. Currently, US Food and Drug Administration–approved PrEP for HIV infection is limited to daily TDF/emtricitabine. Potential alternatives are being evaluated.

There is evidence that rates of sexually transmitted infections (STIs) are high among persons taking PrEP.[7] Thus, it is recommended that follow-up of persons taking PrEP occurs every 3 months to allow for HIV testing and STI screening. Persons taking PrEP who are at risk for HIV infection on clinical grounds or while awaiting HIV RNA confirmation of equivocal screening test results should receive a boosted PI or dolutegravir in addition to TDF/emtricitabine pending viral load and resistance test results.

TDF-based PrEP is not recommended for individuals with osteopenia, osteoporosis, or a creatinine clearance rate below 60 mL/min. TAF/emtricitabine as PrEP must be evaluated in clinical trials.

PEP should be started as soon as possible after exposure to HIV without waiting for confirmation of HIV serostatus or the results of viral load or resistance testing. Recommended PEP regimens are TDF/emtricitabine plus twice-daily raltegravir or once-daily dolutegravir, TDF/emtricitabine plus cobicistat- or ritonavir-boosted darunavir, and elvitegravir/cobicistat/TDF/emtricitabine. PEP regimens should be continued for 28 days. HIV serostatus should be reassessed at 4 to 6 weeks, 3 months, and 6 months after exposure.

Box 6. Recommendations for HIV Prevention[a]

Recommended:

- PrEP for anyone from a population in which HIV incidence is at least 2% per year (AIa) or for HIV-seronegative partners of HIV-infected persons who are not virally suppressed (AIa)
- Daily TDF/emtricitabine for PrEP (AIa)
- Follow-up at intervals of no longer than every 3 months to allow for HIV testing (AIII) and STI screening (BIIb)
- Persons taking PrEP who have suspected HIV infection on clinical grounds or are awaiting HIV RNA confirmation of equivocal screening test results should have a boosted PI or dolutegravir added to TDF/emtricitabine pending HIV RNA and resistance testing results (AIII)
- PEP as soon as possible after HIV exposure without waiting for confirmation of HIV serostatus or results of HIV RNA or resistance testing (AIII)
- TDF/emtricitabine plus twice-daily raltegravir or once-daily dolutegravir, TDF/emtricitabine with cobicistat- or ritonavir-boosted darunavir, or TDF/emtricitabine/cobicistat/elvitegravir for PEP (AIIb)
- PEP regimens should be continued for 28 days, and HIV serostatus should be reassessed at 4 to 6 weeks, 3 months, and 6 months after HIV exposure (AIIb)

Not recommended:

- TDF-based PrEP for individuals with osteopenia or osteoporosis (7III) or a creatinine clearance rate of less than 60 mL/min (AIIa); it should be used with caution in individuals with chronic HBV infection (BIIa)
- TAF/emtricitabine for PrEP until effectiveness has been demonstrated in clinical trials (AIII). Use of non–TDF-containing PrEP or augmentation of PrEP with TDF/emtricitabine with other agents (AIII)

Abbreviations: HBV, hepatitis B virus; PEP, postexposure prophylaxis; PrEP, preexposure prophylaxis; STI, sexually transmitted infection; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from Günthard et al.[1]

[a]Slashes indicate a coformulation.

Future Directions

New therapies for HIV infection must be potent, simple, safe, and tolerable and must fulfill specific needs, such as the need for treatments with activity against multidrug-resistant variants or treatments that are available in long-acting formulations. Investigational long-acting antiretroviral therapy may allow persons who have difficulty with daily oral therapy to maintain viral suppression, may allow for directly observed therapy in clinical or nontraditional settings, and may serve as alternative treatment during periods when oral therapy is difficult. Long-acting antiretroviral treatment and prevention approaches containing rilpivirine, the investigational InSTI cabotegravir, and the investigational microbicide dapivirine (in a vaginal ring) are currently being studied. With long-acting therapies, individuals and retention in care should be closely monitored to avoid risk for the emergence of resistance to treatment.

Broadly neutralizing antibodies are also being studied, and an increasing number of monoclonal antibodies have been identified. These agents, which act to clear replicating virus and infected cells, may have a role in cure strategies and may provide passive immunization to protect individuals at risk for HIV infection. Challenges with these therapies include the need for parenteral dosing, potential development of anti-idiotypic antibodies, and potential resistance to broadly neutralizing antibodies in HIV-infected persons.

The IAS–USA recommendations also discuss cure strategies. In functional cure, HIV infection is controlled without therapy and without the consequences of HIV-related immune activation or inflammation. In eradication cure, all replication-competent virus is purged. Cure strategies must have limited risk, given the safety and effectiveness of current

antiretroviral therapy. Cure strategies being evaluated include the "shock-and-kill" strategy in which latent virus is reactivated and purged from reservoirs; gene therapy, consisting of knocking in protective genes or knocking out susceptible genes; and immune enhancement using therapeutic vaccines and immune checkpoint modulators.

The world of HIV therapeutics has progressed rapidly since the 2014 IAS–USA recommendations on antiretroviral treatment.[8] There are now more potent and convenient regimens available, often as single daily pills, and the potent role these drugs can play in prevention as well as in treatment is recognized. The possibility that the combination of universal treatment and appropriate use of PrEP may bring the HIV epidemic finally under control is exciting, even as the search for a cure continues. These developments will be followed closely and the IAS–USA recommendations will be updated as needed.

Presented by Dr Volberding in August 2016. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Volberding in February 2017.

Financial affiliations in the past 12 months: Dr Volberding has served on data and safety monitoring boards for Merck.

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