



HIV Treatment



Introduction

HIV/AIDS clinical care has improved dramatically over the decades, given the availability of new medications and a better understanding of how best to use antiretrovirals and deliver primary care to persons living with HIV/AIDS. Positive change on such a massive scale, however, brings with it new demands on clinicians.

Along with innovations in HIV drug therapies, HIV/AIDS care has become more complex than ever before due to increasing comorbidities that are attributable to HIV treatment and the aging of the HIV-infected population in the United States. Patient needs also have expanded across a broad spectrum of medical, psychological, behavioral, and social issues. Notably, significant numbers of infected individuals are identified and enter care late in the course of their HIV disease, confronting clinicians with complex and immediate care challenges.

Since the early days of the epidemic, clinicians have received training in HIV/AIDS clinical care through the AIDS Education and Training Centers (AETCs) Program – the clinical training arm of the Ryan White HIV/AIDS Program that is administered by the Health Resources and Services Administration (HRSA) and its HIV/AIDS Bureau (HAB). The AETC network conducts more than 14,000 training events each year with approximately 143,000 health care providers in attendance.

The *Guide for HIV/AIDS Clinical Care* is a pillar of the Ryan White HIV/AIDS Program's mission to continuously improve HIV/AIDS clinical care. The *Guide* was first published in 1993 as a collaborative effort of several regional AETCs. It was subsequently updated and expanded in 2006 and 2011. The version before you incorporates many new insights, but the time-tested format has been retained – easy access to crucial facts for a busy clinician.

The developers of the *Guide* strive to be responsive to how HIV/AIDS clinical care is provided today.

- With more routine HIV testing in medical settings, a large number of individuals are entering care via primary care sites that have relatively limited experience managing HIV/AIDS disease.
- A notable proportion of HIV/AIDS primary care in the United States is provided by advanced practice nurses and physician assistants.
- Shortages in the health care work force are worsening. Experienced staff members are aging and retiring, a limited number of new clinicians are entering primary care and specializing in HIV/AIDS care, and fewer clinicians are available in geographic areas with limited resources.

As a result, front line primary care providers may be less familiar with management of HIV/AIDS disease, as outlined in U.S. Department of Health and Human Services treatment guidelines (available at aidsinfo.nih.gov) and clinical practices presented in this *Guide*.

By presenting best practices in the clinical management of HIV/AIDS disease, the *Guide* can help us continue the remarkable advances in HIV/AIDS care that have made the Ryan White HIV/AIDS Program a model for health care delivery for our Nation and for the world.

Abbreviations for Dosing Terminology

BID = twice daily

BIW = twice weekly

IM = intramuscular (injection), intramuscularly

IV = intravenous (injection), intravenously

PO = oral, orally

Q2H, Q4H, etc. = every 2 hours, every 4 hours, etc.

QAM = every morning

QH = every hour

QHS = every night at bedtime

QID = four times daily

QOD = every other day

QPM = every evening

TID = three times daily

TIW = three times weekly



Antiretroviral Therapy

Background

Potent combination antiretroviral therapy (ART), typically consisting of three or more antiretroviral (ARV) drugs, has greatly improved the health and survival rates of HIV-infected patients in areas of the world with access to ARVs. More than 20 individual ARVs in six classes are available in the United States, in addition to several fixed-dose combination preparations. These can be combined to construct a number of effective regimens for initial and subsequent therapy. Although ART has its limitations (see below), it saves lives and improves immune system function, reduces the risk of many HIV-related and “non-AIDS” complications, and reduces the risk of HIV transmission. Increasingly, several lines of evidence point to the benefit of ART even for patients with high CD4 counts.

Mortality and morbidity benefits of ART are particularly obvious in patients with relatively advanced immune suppression or with symptoms related to HIV infection. For asymptomatic patients with higher CD4 counts (particularly >500 cells/ μL), the question of when to initiate ART remains an area of research and debate. It is clear there is a spectrum of risk for adverse outcomes that increases as the CD4 count declines. In persons with CD4 counts of <200 cells/ μL , effective ART dramatically decreases morbidity and mortality. For persons with CD4 counts of 200-350 cells/ μL , data from randomized controlled studies as well as cohort studies also demonstrate a reduction in both AIDS and non-AIDS events among those who start ART. For patients with higher pretreatment CD4 levels, randomized and cohort studies also have found decreased rates of complications and death in those who initiated ART with CD4 counts of >350 cells/ μL rather than <350 cells/ μL , and some (though not all) observational evidence suggests a mortality benefit of ART among persons with CD4 counts of >500 cells/ μL . For patients with CD4 counts of >500 cells/ μL , the limited data that are currently available (from cohort studies) are inconsistent on the question of whether initiation of ART results in better outcomes. A randomized clinical trial of earlier (>500 cells/ μL) versus deferred (<350 cells/ μL) treatment is under way, and the results of that study along with those from the cohort studies may help define an optimal threshold at which to initiate ART.

Meanwhile, in recent years, a growing body of evidence has demonstrated ongoing and adverse effects of untreated HIV on many organ systems and aspects of functioning, even in persons with high or relatively high CD4 counts (>350 -500 cells/ μL). These include the following:

- Cardiovascular disease
- Kidney disease, specifically HIV-associated nephropathy (HIVAN)
- Liver disease, particularly among patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV)
- Neurocognitive deficits, including dementia
- Cancers, both AIDS-malignancies and non-AIDS malignancies

HRSA HAB Performance Measures

Percentage of clients, regardless of age, with a diagnosis of HIV who were **prescribed antiretroviral therapy** for the treatment of HIV infection during the measurement year

(Core measure)

Percentage of patients, regardless of age, with a diagnosis of HIV with an **HIV viral load of <200 copies/mL** at last HIV viral load test during the measurement year

(Core measure)

Many of these effects appear to be mediated through persistent immune system activation and ongoing inflammation in various organ systems. ART with virologic suppression appears to reduce immune activation and protect against many of these morbidities, but it may not restore immune system function to normal and may not fully reverse disease processes. The beneficial effects of ART may be attenuated for patients who start ART with lower CD4 cell counts. Additionally, the risk of certain ARV-related adverse events may be greater for those who start ART at lower CD4 levels.

Although ART can confer substantial health benefits, it has significant limitations. ART does not cure HIV infection and it requires that multiple medications be taken for life (i.e., potentially many decades). It may cause a variety of adverse effects (some severe), is expensive, requires close adherence to be effective and to prevent the emergence of resistance, and it sometimes fails (because of the patient's imperfect adherence or other factors). The failure of an ARV regimen when accompanied by drug resistance may mean that subsequent regimens are less likely to succeed, despite the availability of second-line ARV combinations.

In past years, many of the available ARVs presented challenges in the realms of adverse effects, pill quantity, dosing frequency, and durability. Given these limitations of ART, much attention was devoted to estimating the point at which the potential benefits of ART outweighed the potential risks of ART. Today, the newer ARV regimens, specifically those currently recommended by the U.S. Department of Health and Human Services (HHS) for initial therapy, are for most patients, simple, tolerable, and effective. As a result of both the availability of ARV regimens that are less toxic and easier to administer, and the increasing appreciation of the adverse impacts of untreated HIV, the balance between the potential benefit and the potential risk of ART has shifted strongly toward treatment for all willing individuals regardless of CD4 count, unless there are compelling reasons not to treat (see "When to Initiate Therapy: HHS ARV Guidelines," below; also see the *HHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* for a full discussion of these issues).

Recent data also demonstrate that ART very substantially reduces the risk of transmission of HIV between serodiscordant heterosexual partners. The prevention effect of ART in men who have sex with men (MSM) and other risk groups has not yet been established in randomized controlled trials, but other lines of evidence suggest that ART strongly protects against HIV transmission in all risk groups. Thus, an additional benefit of earlier treatment with ART is a reduction in the risk of HIV transmission.

Of course, in deciding when to start ART for the individual patient, practitioners must weigh the expected benefits of ART for that person (e.g., improvements in health, reduction in HIV transmission) against the possible risks of ART (e.g., toxicity, drug resistance, adverse drug interactions). Patients must be willing to start and to continue on treatment, with an understanding that high levels of adherence are needed for treatment success.

Although implementing and monitoring ART is complex, a number of guidelines from expert panels are available to help clinicians select effective regimens for particular patients. HHS keeps a repository of frequently updated recommendations on the use of ARV medications for adults and adolescents, pregnant women, and children. All clinicians who treat HIV-infected patients should be familiar with the most current versions of these treatment guidelines. They are available on the Internet at the AIDSinfo website (www.aidsinfo.nih.gov/guidelines). The HHS *Guidelines* are referenced frequently in this chapter.

HHS Guidelines: When to Start Therapy

The following recommendations have been adapted from the HHS *Guidelines*.

HHS guidelines recommend ART for all HIV-infected individuals, both for their own health and to prevent transmission:

“ART is recommended for all HIV-infected individuals to reduce the risk of disease progression. The strength and evidence for this recommendation vary by pretreatment CD4 cell count:”

• CD4 count <350 cells/ μ L:	Strongly recommended
• CD4 count 350-500 cells/ μ L	Strongly recommended
• CD4 count >500 cells/ μ L	Moderately recommended

“ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV. The strength and evidence for this recommendation vary by transmission risks:”

• Perinatal transmission:	Strongly recommended
• Heterosexual transmission:	Strongly recommended
• Other transmission risk groups:	Strongly recommended

Note that these recommendations assume that resources are available for universal ART provision. In settings with limited resources, persons with lower CD4 counts or coexisting conditions (as below) may be prioritized.

ART also is strongly recommended for persons with certain conditions, regardless of CD4 count. These conditions include the following:

- Pregnancy (see chapters *Reducing Perinatal HIV Transmission* and *Care of HIV-Infected Pregnant Women*)

- History of AIDS-defining illness (including HIV-associated dementia)
- HIVAN (see chapter *Renal Disease*)
- HBV coinfection (see chapter *Hepatitis B Infection*)
- Acute HIV infection (see chapter *Early HIV Infection*)

In some situations, ART may be needed relatively urgently. These include the following:

- Pregnancy
- Acute/recent HIV infection
- AIDS-defining conditions
- Acute opportunistic infections
- HIVAN
- HBV coinfection
- HCV coinfection
- Lower CD4 counts (e.g., <200 cells/ μ L)
- Rapidly declining CD4 counts (e.g., >100 cells/ μ L/year)
- Higher viral loads (e.g., >100,000 copies/mL)

S: Subjective

Obtain the patient’s history and review of systems, including the following (see chapter *Initial History*):

- CD4 cell count history, including nadir
- HIV RNA (viral load) history, including pretreatment values if the patient is currently taking ARVs
- History of HIV-related conditions
- Previous and current ARV regimens, including start and stop dates, regimen efficacy, toxicity, resistance
- Current medications, including herbal preparations, supplements, and over-the-counter medications
- Medication allergies, intolerances, or prominent adverse effects

- Comorbid conditions (e.g., HBV, HCV, depression)
- Current and previous substance use, including alcohol and recreational drugs
- Self-assessment of adherence to previous regimens
- Desire to start or continue an ARV regimen
- Commitment to adherence (see chapter *Adherence*)
- Occupation and daily schedule
- Willingness and indicators of ability to adhere to various types of regimens (e.g., QD, BID, with or without food) given current life situation
- For women of childbearing potential: last menstrual period, current method of birth control (if any), current pregnancy status, thoughts on whether or when to have children

O: Objective

Perform the following objective tests:

- Complete physical examination (see chapter *Initial Physical Examination*).
- Current CD4 count and HIV viral load: preferably two or more separate results approximately 1 month apart.
- Drug resistance test, as appropriate; to look for transmitted ARV resistance mutations, a genotype should be performed for all patients before initiating ART; this should be done as early in the course of infection as possible, because mutations may revert to wild-type. Review the results of previous resistance testing or obtain a baseline resistance test, if this was not done earlier; if a test was done in the past, consider retesting before ART is begun (see chapter *Resistance Testing*). Patients on ART whose viral loads are not suppressed also should undergo resistance testing.
- Complete blood count (CBC) and platelet count, liver function tests (LFTs), renal function tests, fasting lipid panel, fasting glucose, rapid plasma reagin (RPR), tuberculin skin test, hepatitis serologies, *Toxoplasma* IgG, urinalysis, (see chapter *Initial and Interim Laboratory and Other Tests*).

A: Assessment

Make the following basic decisions:

- This is or is not an appropriate time to start ART (e.g., do potential benefits of starting at this time outweigh the risks at this time?). See the HHS *Guidelines* noted above, which thoroughly address the issue, and note that many experts are increasingly concerned about the potential harm of untreated HIV infection, even in individuals with high CD4 cell counts. See chapters *Risk of HIV Progression/Indications for ART* and *CD4 Monitoring and Viral Load Testing*.
- The patient is or is not willing to start ARVs at this time (the choice to accept or decline therapy ultimately lies with the patient). If not, work with the patient on readiness issues, with more urgency if the CD4 count is low or the patient has symptoms, comorbidities, or coexisting conditions that suggest treatment is needed.
- The patient is or is not likely to adhere to an ARV regimen (an adherence counselor, with or without a mental health clinician, may be able to assist with this assessment and should be called upon if available). No patient should be automatically excluded from consideration for ART; the likelihood of adherence must be discussed and determined individually (see chapter *Adherence*).

P: Plan

After educating the patient about the purpose and logistics of the proposed regimen and assessing the patient's potential for adherence, ART can be initiated, changed, or postponed accordingly.

The primary goals of therapy are to reduce HIV-related morbidity and mortality and to prevent HIV transmission; this includes improving the quality of life, maximally and durably suppressing HIV virus, and improving immune function and reducing HIV-associated inflammation.

Considerations Before Initiating ART

No “average patient” exists. Some patients will do better during treatment and some will do worse than clinical studies would predict. Health care providers must work with each patient to develop a treatment strategy that is both clinically sound and appropriate for that individual’s needs, priorities, and circumstances of daily life. Despite the fact that the regimens currently recommended by the HHS *Guidelines* are more compact and have fewer adverse effects than earlier regimens, not all patients will be able to take or tolerate all drugs, and the patient’s understanding, readiness to commit to the regimen, and history of adherence to previous regimens must be considered when choosing ARV combinations. Major considerations are as follows:

- Degree of immunodeficiency and risk of disease progression as reflected by the CD4 count and HIV RNA level. ART is more urgent for patients with lower or rapidly declining CD4 counts and also is less likely to be successful in those with low CD4 counts or very high HIV RNA levels (see “HHS Guidelines, When to Start Therapy.” above, and chapters *Risk of HIV Progression/ Indications for ART* and *CD4 Monitoring and Viral Load Testing*)
- Comorbidities
- Potential benefits and risks of ARV drugs
- Resistance, if any, to ARV medications (obtain resistance testing prior to ARV initiation for ARV-naive patients)

Of course, the patient’s willingness to begin ART is critical, as mentioned above. Patients have the right to decline or postpone ART. This

decision should not affect any other aspect of care, and ART should be offered again at each visit to patients for whom treatment is indicated. If mental health issues, addiction, or the patient’s social situation are barriers to adherence, initiate appropriate referrals and reassess adherence barriers at regular intervals.

Preparing the Patient for ART

Before starting ART, it is important to have a detailed discussion with patients about their readiness to commit to a medication regimen, the expected benefits and possible adverse effects, and required monitoring and follow-up visits. Patients must understand that the first treatment regimen offers the best opportunity for effective viral suppression and immune reconstitution, which are primary goals of ART.

Supporting Adherence

Numerous strategies have been tested for their effectiveness in supporting patients’ adherence to the ART regimen. Successful approaches include extensive patient education, telephone contact with office staff members who can answer questions about adverse effects or other difficulties, family meetings, and peer support. Trust and accessibility appear to be important predictors of adherence, and some practitioners see the patient for two or three appointments before starting ART.

Compact regimens consisting of fewer pills and once-daily dosing often encourage adherence. Advise patients about potential adverse effects and at the same time let them know that many adverse effects may be treated or that substitutions often can be made for problematic ARVs. The choice to accept or decline ART ultimately lies with the patient (see chapter *Adherence*).

Anticipating Difficulties

Choosing an initial regimen that fits the patient’s lifestyle and that is likely to be tolerable and easy to take will improve the likelihood of long-term success with that regimen. If patients develop toxicities to one

or more components of an initial regimen, substitutions typically can be made without limiting the success of the regimen. Close monitoring and “check-in” appointments allow these adjustments to be made under clinical supervision. Close monitoring also can help to identify medication toxicities that may limit treatment and to detect early signs of inadequate medication adherence; early intervention to treat adverse effects and to support adherence may increase the likelihood of treatment success.

Considerations in Regimen Selection

Regimens should be selected with consideration of both patient factors and medication factors. The patient’s schedule, adherence history, and self-defined goals of ART should be considered in selecting a regimen to which the patient will adhere closely. The patient’s comorbid conditions and potentially interacting medications should be evaluated for possible contraindications or synergism with ARVs. The ARV history and all resistance profiles should be reviewed carefully so that a regimen that will be likely to achieve durable viral suppression can be chosen. Other factors should be evaluated with regard to specific ARV medications. For example, the HLA-B*5701 status and viral tropism should be determined if abacavir or maraviroc, respectively, are being considered; the HIV RNA level and creatinine clearance (CrCl) should be reviewed if rilpivirine or elvitegravir/cobicistat is being considered, and creatinine and Cr/Cl should be evaluated if tenofovir is being considered. The patient’s HBV status will influence selection of NRTIs (tenofovir + emtricitabine or lamivudine should be included in the ART regimen, for co-treatment of HIV and HBV, unless contraindicated). In women who are pregnant or likely to become pregnant, FDA pregnancy categories and teratogenicity potential for specific ARVs should be taken into account. Drug interactions among ARVs or between ARVs and other medications should be evaluated, as dosage adjustments may be required or certain combinations may be

contraindicated (see relevant tables in the HHS *Guidelines*).

The advantages and disadvantages of various drug classes and individual drugs recommended for use in initial therapy are reviewed in Table 6 of the HHS *Guidelines*.

Use of Multiple Classes of Drugs

For initial therapy in patients with wild-type HIV virus, the HHS *Guidelines* recommend the use of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a nonnucleoside reverse transcriptase inhibitor (NNRTI), a ritonavir-boosted protease inhibitor (PI), or an integrase inhibitor (INSTI). Alternative types of combinations generally do not reduce virus levels as effectively as these recommended types. The question of whether to use an NNRTI, a PI, or an INSTI in initial therapy is a matter of debate. Some clinicians advocate using an NNRTI or INSTI initially to preserve use of the PI class for later and to avoid PI-related toxicities. Others are more concerned about the potential toxicities of NNRTIs or the low genetic barrier to resistance presented by NNRTIs and some INSTIs, and instead recommend starting with a PI-containing regimen. Each of the initial regimens proposed by the HHS *Guidelines* is highly effective if taken as directed, and each has specific advantages and disadvantages (see Table 6 of the HHS *Guidelines*). In the end, the regimen should be selected with the individual patient in mind because the only effective combination for that patient is the one that he or she is willing and able to take on a consistent basis. See the information on drug resistance and toxicities below as well as the full text of the HHS *Guidelines* for more complete discussions.

Salvage therapy for patients with ARV-resistant HIV often comprises agents from three or more ARV classes; consult with an expert.

Boosted Protease Inhibitors

Ritonavir is used at low doses in combination with most other PIs to enhance or “boost” the serum level and prolong the half-life of the PI. This strategy generally decreases the dosing

frequency and the number of pills required, and it improves the activity of some PIs. Several currently used PIs require boosting with ritonavir, and some require ritonavir boosting when used with certain other medications, in order to overcome drug-drug interactions (e.g., atazanavir must be boosted with ritonavir if tenofovir also is a component of the ARV regimen); see “Drug Interactions,” below, and appropriate tables in the HHS *Guidelines*.

Preferred Starting Regimens

More than 20 ARVs in six drug classes have been approved for use in the United States by the U.S. Food and Drug Administration (FDA) (see relevant tables in the HHS *Guidelines*). In recent years, an increasing number of fixed-dose combinations (FDCs) have become available to simplify dosing and reduce pill burden.

These include four NRTI combinations:

- Abacavir + lamivudine (Epzicom)
- Abacavir + lamivudine + zidovudine (Trizivir)
- Tenofovir + emtricitabine (Truvada)
- Zidovudine + lamivudine (Combivir)

One PI coformulation:

- Lopinavir + ritonavir (Kaletra)

And three one-pill-per-day formulations of two NRTIs + one NNRTI or one INSTI:

- Efavirenz + tenofovir + emtricitabine (Atripla)
- Rilpivirine + tenofovir + emtricitabine (Complera)
- Elvitegravir + cobicistat + tenofovir + emtricitabine (Stribild)

Other FDCs are in development and may become available in coming years.

The HHS *Guidelines* suggest “preferred” and “alternative” components for initial therapy (Table 1). Clinicians should note that these recommendations change over time as new data regarding efficacy or toxicity become

available and should refer to the most up-to-date HHS guidelines. Among regimens with adequate potency (taking into account possible ARV resistance), regimen selection should be guided by factors such as anticipated tolerability, pill burden, drug interactions, and the patient’s comorbid conditions.

Table 1. Recommended Regimens for Initial Antiretroviral Treatment

Preferred Regimens	
NNRTI based	Efavirenz ¹ /tenofovir/emtricitabine ²
PI based	Atazanavir/r + tenofovir/emtricitabine (TDF/FTC) ² Darunavir/r (QD) + TDF/FTC ²
INSTI based	Raltegravir + TDF/FTC ² Elvitegravir/cobicistat/TDF/FTC ^{2,3} Dolutegravir (QD) + abacavir/lamivudine (ABC/3TC) ^{2,4} Dolutegravir (QD) + TDF/FTC ²
Alternative Regimens	
NRTI based	Efavirenz ¹ + ABC/3TC ^{2,4} Rilpivirine ⁵ /TDF/FTC ² Rilpivirine ⁵ + ABC/3TC ^{2,4}
PI based	Atazanavir/r + ABC/3TC ^{2,4} Darunavir/r + ABC/3TC ^{2,4} Fosamprenavir/r (QD or BID) + ABC/3TC ^{2,4} or TDF/FTC ² Lopinavir/r (QD or BID) + ABC/3TC ^{2,4} or TDF/FTC ²
INSTI based	Raltegravir + ABC/3TC ⁴

¹ Efavirenz is teratogenic in nonhuman primates. Strongly consider alternative agent for women who plan to become pregnant or are not using effective and consistent contraception.

² 3TC can be used in place of FTC and vice versa.

³ Should be considered only for patients with estimated CrCl ≥70 mL/min.

⁴ Abacavir should not be used by patients who test positive for HLA-B*5701; use with caution if HIV RNA level is >100,000 copies/mL or if there is a high risk of cardiovascular disease.

⁵ Rilpivirine is not recommended if the pretreatment HIV RNA is >100,000 copies/mL; caution if the CD4 count is <200 cells/μL.

Abbreviations: /r = low-dose ritonavir; INSTI = integrase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide analogue; PI = protease inhibitor
Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. Available at www.aidsinfo.nih.gov/guidelines. Accessed December 1, 2013.

Note: Many other ART combinations are possible, and in some cases a different option may be most appropriate for the individual patient. The HHS *Guidelines* also list regimens that are “Acceptable,” those that “May be acceptable,” but are “less satisfactory” or lack definitive data, and several that “May be acceptable but should be used with caution”; see Table 5b in the HHS *Guidelines*.

Once-Daily Regimens

The use of convenient and simplified dosing is an obvious strategy for improving adherence, particularly with the availability of coformulations that reduce pill burden (see “Preferred Starting Regimens,” above). The HHS *Guidelines* emphasize the importance of simple regimens and currently include six once-daily combinations among “preferred” regimens for initial therapy, and list a number of other possibilities among “alternative” regimens.

Avoiding Drug Resistance

ARV medications never should be given as single agents, in two-drug regimens, in suboptimal regimens, or in lower dosages than recommended, because of the potential for development of resistance. High-level resistance to NNRTIs, as well as to emtricitabine and lamivudine, may develop quickly (i.e., within days to weeks) in these situations, and the same may be true for the INSTIs raltegravir and elvitegravir. It may take longer for high-level resistance to develop to other NRTIs and to ritonavir-boosted PIs, and perhaps also the INSTI dolutegravir. Patients must be instructed to take the full dosage of all medications on schedule and to avoid skipping doses or taking “days off” from their regimens. Careful medication dosing is important because resistance to one drug within a particular class may transfer to other drugs in the same class (cross-resistance). Cross-resistance can limit the options for future therapy significantly or necessitate the use of very complicated regimens in the future. Once resistant viral strains have developed, they may be transmitted to other people.

Acquired or “primary” resistance, in which a patient is infected with ARV-resistant virus, is common in parts of the United States. Because both multi- and single-class resistance has been found among ARV-naive persons in many U.S. cities, it is recommended that individuals with newly diagnosed HIV infection and all others entering care should receive a baseline resistance test. This test should be obtained as early as possible, in order to maximize the likelihood of detecting transmitted mutations, and before initiation of ART (see chapter *Resistance Testing*).

Drug Interactions

Many of the ARVs interact with one another as well as with other common medications. When starting or changing an ARV regimen, review all the patient’s current medications carefully for possible drug interactions. See chapter *Drug-Drug Interactions with HIV-Related Medications* for a summary of this issue and for references and resources to review medication lists and combinations. For further information on drug interactions involving ARVs, see relevant tables in the HHS *Guidelines*.

Drugs and Drug Combinations That Should Not Be Used

Most clinicians in the United States avoid using the NRTIs zidovudine (except for pregnant women), stavudine, or didanosine if other options are available, because of the high rates of metabolic and other adverse effects associated with these agents. Stavudine, in particular, is likely to cause peripheral neuropathy and lipoatrophy. Drugs with additive or overlapping toxicities, such as stavudine and didanosine, should not be combined. Zidovudine and stavudine, which compete intracellularly and therefore cause antagonism, should not be used together.

Drugs with similar mechanisms of action and resistance mutations (e.g., lamivudine and emtricitabine, or efavirenz and nevirapine) offer no significant advantage when combined and may increase toxicities. Certain drug

combinations have suboptimal efficacy and are not recommended (e.g., tenofovir + didanosine as an NRTI backbone; three-NRTI regimens). Some ARVs require specific dosing intervals in particular patients. For example, once-daily dosing of lopinavir/ritonavir is not recommended for patients receiving concomitant efavirenz or nevirapine, and some once-daily PIs or combinations should not be used for treatment-experienced patients. For further information, see relevant tables in the *HHS Guidelines*.

Follow-Up of Patients Starting ART

Patients who start a new ARV regimen ideally should be seen at least twice within the first month to allow for an assessment of their adherence to therapy and the tolerability and adverse effects of the regimen.

When patients have been on a new regimen for 2-8 weeks, clinicians should check the following:

- HIV viral load, to monitor initial virologic response to therapy, then every 4-8 weeks until the viral load is below the level of detection
- CBC with platelets, for patients starting a zidovudine-containing regimen, to monitor for anemia
- LFTs, to monitor for hepatotoxicity (patients starting a nevirapine-containing regimen should be monitored closely for the first 18 weeks of treatment)
- Serum electrolytes, blood urea nitrogen, and creatinine (particularly for patients taking tenofovir)
- Fasting glucose and lipids (after 1-3 months)

CD4 cell count should be checked after about 3 months.

For further information, and for recommendations about monitoring stable patients, see chapter *Initial and Interim Laboratory and Other Tests*.

Regimen Failure

An ART regimen may fail for several reasons, including the following:

Incomplete virologic response

- Viral load is >200 copies/mL on consecutive tests after 24 weeks on therapy. (For some patients with multidrug resistance, it may not be possible to decrease plasma HIV viral load to undetectable levels, and stabilization of viral load below the previous baseline may be an appropriate goal of therapy.)

Virologic rebound

- Virus is repeatedly detected in plasma (>200 copies/mL) after suppression to undetectable levels. Confirmatory testing is required to rule out “blips” of virus (isolated elevations in viral load of less than several hundred copies/mL) that are not clinically significant and to ensure that the increase is not caused by infection, vaccination, or problems with test methodology. Note that some patients may have persistently detectable low-level viremia (<200 copies/mL); the clinical significance of this is not clear.

Immunologic failure

- Despite virologic suppression on ART, the CD4 cell count shows an inadequate response or a persistent decline.

Clinical progression

- Recurrent, persistent, or new HIV-related illness occurs after ≥3 months on ART. Note that new or recurrent symptoms of opportunistic illness occurring in the first weeks to months after starting ART, especially in patients with severe immunosuppression, may not reflect a failure of ART. Rather, these symptoms could be attributable to persistence of opportunistic infections that may require longer treatment, or they could be caused by an immune reconstitution inflammatory syndrome (see chapter *Immune Reconstitution Inflammatory Syndrome*).

Responding to Apparent Treatment Failure

- Carefully assess patient adherence, because inadequate adherence to ART is a common reason for regimen failure. In some cases, adherence support, treatment of adverse drug effects, substitution for poorly tolerated ARVs, or other measures to enhance adherence may result in virologic suppression (see chapter *Adherence*). In other cases, ARV resistance may have developed. Poor adherence may affect the decision to change therapy, and adherence issues should be addressed before a new regimen is initiated. If resistance is suspected, obtain an appropriate resistance test (or CCR5 tropism assay, if the patient is taking a CCR5 antagonist) while the patient is on the failing regimen; see below.
- The availability of effective alternative ARVs is a critical consideration in deciding whether or when to change therapies. The development of new ARVs and new ARV classes in recent years has made virologic suppression possible for most patients, even those with extensive resistance. For the few patients in whom treatment possibilities are limited or nonexistent, it may be necessary to weigh the value of partial virologic suppression with the current regimen against the likelihood of further resistance developing. Strongly consider consultation with an experienced HIV provider and the use of HIV resistance testing when considering changes in therapy. When no treatment options remain among currently approved drugs, refer the patient to an appropriate clinical trial, if possible.

Note that the optimal management of immunologic failure is uncertain and is an active area of research. Consult with an HIV expert and consider referral to a research study.

Resistance and Coreceptor Tropism Testing

If resistance is suspected, obtain an appropriate resistance test (see chapter *Resistance Testing*). Resistance testing is recommended, before changing regimens, in cases of virologic rebound during ARV therapy or suboptimal suppression of viral load on ARV therapy. Resistance testing often is crucial in identifying ARVs that are not likely to be effective against the patient's virus. It should be done while the patient is taking the failing regimen (or within 4 weeks of discontinuation) to maximize the likelihood that resistant viral populations will be present in detectable numbers. In virologic failure of a first regimen, it is fairly common to see resistance to only one or two drugs in a multidrug combination. The test results should be interpreted in the context of the patient's ARV history and the results of previous resistance tests.

Standard genotypes test give information about resistance that may affect NRTI, NNRTI, and PI agents. If INSTI (or fusion inhibitor) resistance is suspected, a specific genotype test must be ordered. For patients with virologic failure while taking a CCR5 antagonist, a coreceptor tropism assay should be obtained (though the result does not rule out the possibility of resistance to CCR5 antagonists).

Cross-resistance exists among ARVs, such that resistance to one drug in a class of agents often extends to other drugs in that class. For example, cross-resistance between efavirenz and nevirapine is almost complete, and resistance mutations to NRTIs, INSTIs, and PIs often decrease viral susceptibility to other drugs in those classes. As a result, selecting a new ARV regimen can be complicated because it requires knowledge of expected resistance patterns. The likelihood of sustained viral suppression is lower when resistant virus is present, unless three ARVs that are fully active against the patient's virus can be included in the subsequent regimen.

If treatment with a CCR5 antagonist is being considered, a tropism test must be obtained to verify that the patient has only CCR5-tropic virus (the currently available agent in this class is not effective in patients with any degree of CXCR4 virus). The standard test requires an HIV viral load of >1,000 copies/mL at the time of testing; a newer proviral DNA assay can identify coreceptor tropism in blood samples with HIV RNA levels below the limit of detection (this has not been clinically validated).

Suggestions for Changing an ARV Regimen for Suspected Drug Failure

The following recommendations are adapted from the HHS *Guidelines*.

Distinguish between the need to change a regimen because of drug intolerance or inability to adhere to the regimen and the failure to achieve the goal of sustained viral suppression. In the event of intolerability, single agents usually can be changed without resistance testing.

In general, do not change a single drug or add a single active drug to a failing regimen; it is important to use at least two or, preferably, three fully active ARVs (e.g., ARVs selected on the basis of resistance testing or because they are from a drug class to which the patient's virus has not been exposed). If resistance testing (performed while the patient is taking the failing regimen) shows resistance to only one agent in a regimen, it may be possible to replace only that drug; however, consultation with an expert is recommended.

In general, the goal of ART is to suppress HIV RNA to undetectable levels, in order to improve or maintain immune function. This usually is possible even for patients with resistance to multiple drugs as new ARV agents and new classes of ARVs have become available. Nevertheless, some patients have

limited options for new regimens that will achieve durable virologic suppression. In some of these cases, it may be reasonable to continue the same regimen if partial virologic suppression and clinical and immunologic stability are maintained. The risk of continuing patients on a partially suppressive regimen, however, is the emergence of additional resistance mutations.

Data on the value of restarting a drug that the patient has previously received are limited. Resistant virus can be archived and will reemerge for patients who are rechallenged with regimens on which they had previously developed resistance. As a result, resistance tests from previous regimens should be used with current resistance tests to determine what drugs might be active in a new regimen.

Making the decision to change therapy and choosing a new ARV regimen require that the clinician have considerable expertise in the care of people with HIV infection. Those less experienced in the care of persons with HIV are strongly encouraged to obtain assistance by consulting with or referring to an expert.

Follow-Up of Patients Not Started on ART

Patients who are not on ART

These patients should continue their regular visits for monitoring, prophylaxis, and other medical treatment (see section *Testing and Assessment* for chapters on physical examinations and laboratory tests). ART should be discussed again and offered at regular intervals to anyone who initially refuses treatment. Routine clinic visits present ongoing chances to discuss the benefits of ART and the risks of delayed treatment, and to educate patients about new medications and research findings. Decreases in patients' CD4 count or declines in their condition should be taken as opportunities to reassess their decisions about ARVs. If lack of readiness or

probable adherence difficulties are at issue, an adherence counselor (if available) or a mental health provider should be engaged to bolster the patients' support and coping mechanisms (see chapter *CD4 Monitoring and Viral Load Testing* and the *HHS Guidelines*).

Special Situations for ART

ART during acute or recent HIV infection

There are no definitive data that demonstrate long-term benefit if ART is started during early HIV infection, though emerging clinical data as well as theoretical considerations suggest early treatment may reduce the severity of immune system disruption and lessen both the short-term and the long-term impact of HIV infection. In addition early treatment may decrease the risk of HIV transmission during the highly infectious period of acute HIV.

The *HHS Guidelines* recommend treatment of acute HIV (if identified during pregnancy, ART should be started as quickly as possible to reduce the risk of perinatal HIV transmission). Before starting an ARV regimen, patients must be counseled carefully about potential limitations, such as toxicity, pill burden, cost, and the possible development of drug resistance. Patients should be monitored with HIV viral load, CD4 counts, and other parameters, as with patients with established infection who are receiving ART. See chapter *Early HIV Infection*.

Pregnant women

Combination ARV regimens are recommended for all women during pregnancy, regardless of CD4 count or HIV RNA level. The goal of ART for pregnant women is to reduce the risk of transmission to the infant and to treat HIV infection in the mother, through maximal virologic suppression. Obviously, the decision of whether to start ART during pregnancy is the choice of the woman, and her choice must be respected. There are a number of

specific considerations about ART for pregnant women, including the timing of ART initiation (for those not already on treatment), specific ARVs that are recommended or that should be avoided (because of toxicity or teratogenicity concerns), pharmacokinetic variations and dosing requirements in pregnancy, and indications for resistance testing. See chapters *Reducing Perinatal HIV Transmission* and *Care of HIV-Infected Pregnant Women*; also refer to the *HHS Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*.

Older persons

Older persons with HIV infection may experience earlier development of a number of conditions that are associated with aging, such as cardiovascular disease and neurocognitive impairment. Additionally, older persons may have dampened immunologic responses to ART. For these reasons as well as others, ART initiation in older persons probably should not be delayed. Current *HHS Guidelines* recommend ART for all patients older than 50 years of age.

Acute opportunistic infections

The presence of opportunistic infections is a strong signal of the need for ART and effective immune reconstitution. For some of these infections, ART is the primary therapy, and for others it is adjunctive. Although ART sometimes causes immune reconstitution inflammatory syndromes if initiated in the setting of acute opportunistic infection, clinical data for many such infections (including *Pneumocystis jiroveci* pneumonia and tuberculosis in persons with very low CD4 counts) suggest improved outcomes, including better survival, if ART is started early. Exceptions to this recommendation include cryptococcal meningitis, for which most experts recommend a short period of antifungal treatment before ART is started.

For further information, see chapter *Immune Reconstitution Inflammatory Syndrome* and the *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America* (see “References,” below).

Hepatitis B coinfection

If treatment for either HIV or HBV is to be started, both infections generally should be treated simultaneously, by including in the ART regimen two NRTIs with activity against both viruses (tenofovir + emtricitabine or tenofovir + lamivudine), if possible. The use of a single NRTI with activity against both viruses (resulting in monotherapy for HBV) is not recommended. If tenofovir is contraindicated, another anti-HBV drug should be used in combination with lamivudine or emtricitabine. Flares of HBV may occur if tenofovir, emtricitabine, or lamivudine is discontinued; monitor closely or consider substitution of another anti-HBV drug. See chapter *Hepatitis B Infection* and the HHS *Guidelines* for additional information.

HIV-associated nephropathy

ART is a primary treatment for HIVAN and should be started urgently for patients with suspected HIVAN. See chapter *Renal Disease*.

Expert Consultation

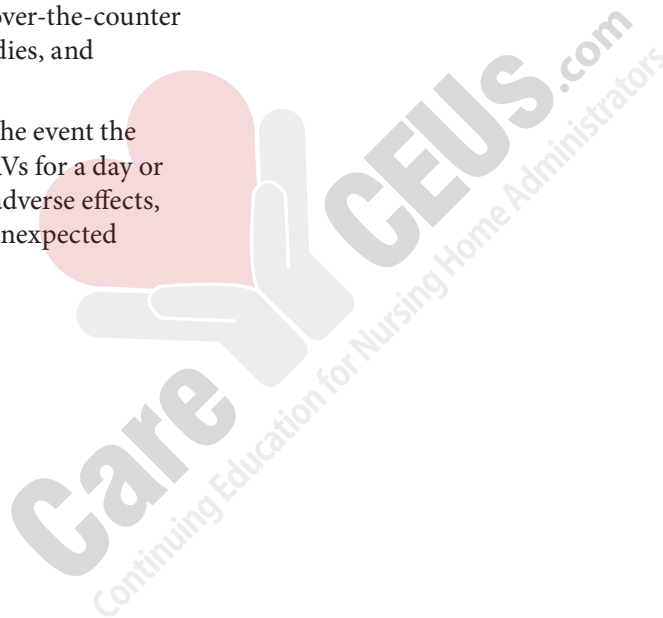
The National HIV/AIDS Clinicians' Consultation Center is a valuable resource for any clinician seeking expert advice about ART, HIV clinical manifestations, laboratory evaluations, and other issues. Its National HIV Telephone Consultation Service (Warmline) is staffed by HIV-experienced physicians and pharmacists. The Warmline operates Monday through Friday, 9 a.m. to 8 p.m. eastern time and is available free of charge in the United States at 800-933-3413.

Patient Education

- Making the decision to start ART is rarely an emergency situation. Before starting patients on ART, health care providers must work with them to determine what goals of therapy are likely to be achieved, and which personal issues are pertinent for selecting the best regimen to fit their lifestyles,
- Providers should review the proposed drug regimen with their patients. Be sure patients understand the instructions about dosage, scheduling, food requirements or restrictions, drug storage, adverse effects, toxicities, and type of reactions that must be reported immediately, as well as remedies for common adverse effects.
- Providers should explain to patients that successful ART requires a commitment to taking the medications every day, as prescribed. If ARVs are taken incorrectly, HIV can quickly become resistant to the medications. This will mean even fewer choices and less-effective treatment in the future. It also may mean that patients could transmit resistant virus to a partner or, if they are pregnant, to an infant.
- Patients should know that HIV medications may reduce the risk of HIV transmission substantially but do not offer perfect protection against infecting others. Recommend prevention measures such as using latex barriers during sex (safer sex) and not sharing needles or other drug-using equipment, even with other HIV-infected persons (see chapter *Preventing HIV Transmission/Prevention with Positives* for more information).
- HCV, HBV, and other sexually transmitted diseases such as syphilis and gonorrhea can be transmitted between two HIV-infected partners.
- Patients should be advised to check with their provider before discontinuing ARVs.

If ARVs must be discontinued, it is usually best to stop all ARVs at once. The exception to this recommendation may be NNRTI-containing regimens. In this case, blood levels of the NNRTIs may be detectable for several weeks after discontinuation; if NRTIs are stopped, that may result in NNRTI monotherapy and the risk of NNRTI resistance. The optimal strategy for discontinuing NRTIs is not clear; some experts recommend continuing the NRTIs for a period of time after discontinuation of the NNRTI or switching from an NNRTI to a PI for some time before stopping all agents.

- Patients should be encouraged to advise their provider of all other medications that they take, including over-the-counter medications, herbal remedies, and nutritional supplements.
- Discuss contingencies in the event the client is unable to take ARVs for a day or more (e.g., illness, severe adverse effects, hospitalization, or other unexpected circumstances).



Reducing Perinatal HIV Transmission

Background

This chapter describes strategies for reducing the risk of perinatal HIV, based on the U.S. Department of Health and Human Services (HHS) *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. It is not intended to be a comprehensive discussion of these topics, and all HIV-infected pregnant women should be treated by an HIV-experienced obstetrician and an HIV specialist. For centers that do not have HIV specialists available, experts at the National Perinatal HIV Consultation and Referral Service are available for consultation through the Perinatal HIV Hotline (888-448-8765). For more information on other aspects of caring for HIV-infected pregnant women, see chapter *Care of HIV-Infected Pregnant Women*.

Unless otherwise referenced, the information in this chapter is based on the most recent HHS perinatal guidelines available at the time this chapter was published. Consult the AIDSinfo website (aidsinfo.nih.gov/guidelines) for the most current recommendations.

Overview of Prevention of Perinatal HIV Transmission

In the absence of antiretroviral (ARV) prophylaxis or other interventions, the rate of perinatal HIV transmission in the United States ranges from 16% to 25%. Antiretroviral therapy (ART) is highly effective in reducing the risk of perinatal transmission of HIV, to as low as <1%. It probably prevents HIV transmission in several ways, including by reducing the mother's viral load in blood and genital secretions and by providing pre- and postexposure prophylaxis for the infant. All pregnant women with HIV infection should be educated about the risks of perinatal HIV transmission and offered ART and other medical management to maintain or improve their own health and to reduce the risk of HIV transmission to their infants.

In 1994, the Pediatric AIDS Clinical Trial Group study 076 (PACTG 076) found that ARV treatment during pregnancy could significantly reduce the risk of HIV transmission to infants. The intervention, consisting of zidovudine (ZDV) given PO to the women during the last weeks of pregnancy and IV during labor

and delivery, as well as to the newborns for 6 weeks, reduced the rate of infant infection from 25.5% to 8.3%. The ZDV regimen quickly became the standard of care in the United States and other high-income countries. Subsequent studies showed that combination ARV regimens with suppression of maternal HIV viral load to undetectable levels further reduced the risk of perinatal infection.

Studies in resource-limited countries as well as in resource-abundant areas have examined various ARV strategies for reducing the risk of perinatal HIV transmission. The Petra study, a placebo-controlled trial in a breast-feeding population in Uganda, South Africa, and Tanzania, found a transmission rate of 8.9% among women who received PO ZDV plus lamivudine (3TC) intrapartum and for 1 week postpartum and whose infants also received 1 week of ZDV/3TC, compared with a rate of 15.3% in the placebo group. The HIV NET 012 trial in a breast-feeding population in Uganda compared the efficacy of a single dose of nevirapine (NVP) given to the mother at the onset of labor plus a single dose given to the newborn 48 hours postpartum with that of PO

ZDV given to the mother during labor and to the newborn. The transmission rate was 11.8% in the NVP arm, compared with 20.0% in the ZDV arm. The results of this study and the low cost of NVP prompted a number of resource-limited countries to institute NVP prophylaxis as the standard of care for preventing mother-to-child transmission of HIV. Numerous other trials have demonstrated the efficacy of various ARV strategies, combining different ARVs with different treatment durations and given to mothers, newborns, or both, in both breast-feeding and non-breast-feeding populations. Research has shown that ARV interventions even late in the peripartum or newborn periods may decrease the infant's risk of HIV infection. A retrospective study of subjects in New York found that the rate of perinatal HIV transmission was 9.3-10% if ZDV was given either to both the mothers intrapartum and their newborns or to the newborns only, compared with 26.6% if no ARV medication was given. This study underscores the importance of offering ARV interventions to pregnant women with HIV infection whenever they are identified during pregnancy or during labor and delivery, or as an intervention with the newborn.

In the United States, the PACTG 076 regimen remains an important component in the prevention of perinatal HIV transmission, and usually is incorporated into combination ART for pregnant women. For international settings, other guidelines have been developed by global agencies such as the World Health Organization (see "References," below) and by individual governments.

Mother-to-child transmission also can occur through breast-feeding. Recent studies have shown that ART given to the nursing mother and/or her infant decreases but does not eliminate the risk of HIV transmission to the infant. In the United States, because substitute feeding is safe, affordable, feasible, sustainable, and available, mothers in the United States should not breast-feed.

HIV Testing During Pregnancy

The success of interventions to reduce the risk of perinatal HIV transmission has been achieved through the routine HIV testing and counseling of all pregnant women. Interventions to prevent transmission can be effective only if women know their HIV status and have access to treatment. HHS has recommended universal HIV counseling and testing for pregnant women since 1995. Many national professional and governmental organizations, including the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force, endorse those recommendations. Current recommendations from the U.S. Centers for Disease Control and Prevention (CDC) feature the following three approaches to HIV testing during pregnancy:

- Routine testing as part of first-trimester prenatal screening tests for all pregnant women, using an "opt-out" policy whereby a pregnant woman is tested unless she specifically declines testing
- Routine "opt-out" testing with a rapid HIV test for women who present in labor with unknown or undocumented HIV status, in order to offer ARV prophylaxis during labor for those who test positive for HIV
- Expedited HIV testing for newborns of mothers of unknown HIV status so that they can receive postexposure ARV prophylaxis, if indicated

The CDC also recommends repeat HIV testing in the third trimester for women who receive health care in jurisdictions with an elevated incidence of HIV or AIDS among women, as well as for women at high risk of acquiring HIV (e.g., a history of injection drug use, exchange of sex for money or drugs, multiple sex partners, or a partner known to be HIV infected). Jurisdictions in which repeat third-trimester testing is recommended include Alabama, Connecticut, Delaware,

District of Columbia, Florida, Georgia, Illinois, Louisiana, Maryland, Massachusetts, Mississippi, Nevada, New Jersey, New York, North Carolina, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, Tennessee, Texas, and Virginia. A number of states mandate a third-trimester HIV test for all pregnant women.

Any pregnant woman with signs or symptoms of acute HIV infection should be evaluated (see *chapter Early HIV Infection*) and receive an HIV plasma RNA test as well as an antibody test.

State laws regarding HIV testing during pregnancy vary widely, and many are currently under review. A number of states have adopted the opt-out approach, whereas some still require written informed consent before an HIV test is done. Others require patient education and a chart note from the providers. Clinicians should be familiar with relevant state laws regarding HIV testing during pregnancy, opt-out or consent provisions, and regulations about rapid HIV testing during the intrapartum or newborn period. (Information on state laws regarding HIV testing during pregnancy can be found at the National HIV/AIDS Clinicians' Consultation Center's Compendium of State HIV Testing Laws at www.nccc.ucsf.edu.) Whatever the consent process, a woman should know that an HIV test is being done and should receive at least the information outlined below.

HIV Education and Counseling of Pregnant Women

Educating pregnant women about the importance of HIV testing is a critical element in preventing perinatal HIV transmission. However, extensive pretest counseling is not essential. A woman must be told that HIV testing is a standard component of prenatal care, that her clinician recommends the tests, and that all pregnant women should be tested for HIV because knowing about HIV infection is important for their health and the health of their babies. Research has

shown that a provider's strong endorsement of HIV testing is a major predictor of whether a woman receives an HIV test. Testing should be voluntary and free of coercion, and a woman should know that she can decline testing without the risk of being denied care. A woman's age, cultural background, educational level, and primary language may influence her knowledge about HIV transmission and her willingness to be tested; the clinician should consider these factors carefully when providing education and information.

The following minimum information should be provided through an educational session with a health care provider or through written or electronic media (e.g., brochures, videos):

- HIV is the virus that causes AIDS.
- Without treatment, approximately 25% of babies born to HIV-infected women will be infected, either during pregnancy, during labor and delivery, or by breast-feeding.
- A woman could be at risk of HIV infection and not know it.
- ART is highly effective in protecting the infant from being infected with HIV and can improve the mother's health.
- HIV testing is recommended for all pregnant women.
- Women who decline testing will not be denied care.

Women should be told that test results are confidential to the extent allowed by law and that medical and other services are available for women with HIV infection. Reporting requirements for the specific state should be explained.

HIV testing should be performed as early in pregnancy as possible to allow for interventions to prevent transmission and for effective management of a woman's HIV infection, if the woman is found to be HIV seropositive. The CDC recommends repeat HIV testing in the third trimester for women who have risk factors for HIV or who live in

areas with a high incidence of HIV in women; some states mandate third-trimester testing for all pregnant women.

If the client declines testing at any point, the clinician should inquire about her reasons and follow up at subsequent visits. If the provider is persistent, the woman may choose to have an HIV test at a later visit.

In the United States, the vast majority of pregnant women who are tested for HIV will be HIV seronegative. When giving test results to an HIV-negative woman, the clinician should take the opportunity to discuss risk-reduction strategies to help ensure that she remains uninfected by HIV. Women at risk of HIV infection should be referred for more extensive counseling because some research indicates that pregnancy may place them at greater risk of acquiring HIV infection, and acute HIV infection may confer greater risk of transmission to the fetus.

Counseling a pregnant woman with a positive HIV test result requires knowledge and sensitivity. The clinician should explain that, even though the woman may feel well, she is infected with the virus. The woman should be told about the importance of medical management of HIV for her own health and for the prevention of perinatal transmission, and she should be guided to the medical and social services available in her local community. She also should be referred to an HIV obstetric specialist who can work closely with her primary obstetric and HIV providers to manage her care during the pregnancy. The patient may be surprised or shocked upon receiving the HIV diagnosis, or she may have known her status but been reluctant to disclose it. The clinician should emphasize the importance of emotional and social support, assess the patient's social support resources, and offer her referrals as needed.

Expedited HIV Testing During Labor

As discussed earlier, beginning ART during pregnancy offers the greatest chance for preventing perinatal transmission of HIV, but interventions during the intrapartum and neonatal periods also offer opportunities to decrease the risk of HIV transmission.

Expedited HIV testing for women who present in labor with unknown or undocumented HIV status can identify women who are infected with HIV so that interventions can be offered. Available rapid HIV antibody tests are both sensitive and specific and provide results in as little as 20 minutes. Fourth-generation antigen-antibody HIV tests also are becoming increasingly available through hospital laboratories using random access machines that deliver results in 30 minutes to 2 1/2 hours.

Women who should receive HIV testing during labor include the following:

- Those who have had little or no prenatal care
- Those who were not offered testing earlier in pregnancy
- Those who declined previously
- Those whose HIV test results are not available at the time of labor

Education and counseling for the woman in labor who needs an HIV test should incorporate the information for prenatal education discussed earlier, with consideration given to the special circumstances of labor. Special educational formats such as flip charts have been developed to help with patient education. Confidentiality should be assured for the information and consent process and for treatment. If an opt-out approach is used in the labor setting, a woman of unknown serostatus should be told that no HIV test is found on her chart, that HIV testing is part of routine care, and that she can decline if she wishes, but that experts recommend HIV testing because available interventions can

decrease her baby's risk of becoming infected with HIV if she is found to be seropositive.

Women who present in labor with unknown HIV serostatus should undergo expedited HIV antibody testing. If the results are positive, a confirmatory HIV test should be sent as soon as possible but maternal prophylaxis should be started immediately (intravenous ZDV). This should be followed by combination ARV prophylaxis (ZDV + NVP) for the infant beginning as soon as possible after birth. ARV drugs should be initiated pending results of the confirmatory test. If the confirmatory HIV test result is positive, infant ARV drugs should be continued for 6 weeks. If the confirmatory test result is negative, the infant ARV drugs should be stopped.

Factors Influencing Perinatal HIV Transmission

Perinatal transmission is most likely to occur in the intrapartum period. Several factors influence the risk of transmission from mother to infant. One of these is the mother's HIV RNA level (viral load). Clinical trials and observational studies have shown a strong positive correlation between maternal HIV viral load during pregnancy or during delivery and the risk of perinatal HIV transmission, even among women receiving treatment with ARVs. However, HIV transmission may occur at any level of maternal HIV RNA, including (rarely) when the viral load is undetectable. HIV RNA levels in the blood and the genital tract generally correlate but discordance may occur. Low-level cervical-vaginal HIV shedding has been found even in women on ART with undetectable plasma HIV RNA, particularly in the presence of genital infections.

ARV prophylaxis is a critical factor in reducing HIV transmission. For women on effective combination ART with undetectable HIV RNA, the rate of perinatal HIV transmission is approximately 1%. Thus, ARV prophylaxis

with full suppression of HIV RNA is recommended for all pregnant women with HIV infection, regardless of HIV viral load. Note that ART may exert protective effects not only by lowering maternal HIV RNA but also (for ARVs with good transplacental passage) by providing pre- and postexposure prophylaxis for the infant.

Other maternal factors associated with increased risk of perinatal transmission include low CD4 cell count, sexually transmitted diseases, active genital herpes during labor, illicit drug use, cigarette smoking, and unprotected sex with multiple partners.

Obstetric factors also affect the risk of HIV transmission. Infection risk increases linearly with the increased duration of ruptured membranes, although the effect of ruptured membranes in women with low viral loads is not known. Invasive procedures performed at any time during pregnancy, such as amniocentesis, placement of scalp electrodes, artificial rupture of membranes, episiotomy, or operative (forceps) delivery may increase risk by exposing the fetus to maternal blood; these procedures should be avoided (though the risk of transmission in women on fully suppressive ART is not clear). In addition, the mode of delivery, whether vaginal or cesarean, can influence the risk of HIV transmission. Scheduled cesarean delivery decreases the rate of perinatal infection for women with an HIV RNA level of >1,000 copies/mL, but its efficacy is not clear for women whose labor has begun or for those whose membranes have ruptured; see "Intrapartum Management and Mode of Delivery," below, for further information.

Infant risk factors for HIV infection include premature birth, low birth weight, skin and mucous membrane lesions such as thrush, and breast-feeding. Breast-feeding increases the risk of HIV transmission by 5-20%. In the United States, where safe, affordable replacement feeding and clean water routinely are available, women with HIV should not breast-feed.

However, some women with HIV will be under tremendous cultural and familial pressure to breast-feed and will need the clinician's ongoing support to use substitute formula.

Because many factors that affect the risk of perinatal HIV transmission may be modified, clinicians should educate pregnant women carefully about the importance of ARV prophylaxis and other strategies to reduce the risk of maternal-fetal transmission of HIV.

Antiretroviral Therapy During Pregnancy

The goals of ART for the pregnant woman are the same as those for any person living with HIV:

- To suppress the level of HIV as low as possible for as long as possible
- To preserve and restore immune function
- To prolong life and improve quality of life
- To reduce risk of HIV transmission to sex partners

An additional, and crucial, goal of ART for pregnant women is to reduce the risk of perinatal HIV transmission through maximal HIV suppression.

The HHS recommendations discuss in detail the multiple issues that must be considered when balancing the woman's need for therapy for her own health and the need to decrease the risk of transmission to the infant. Combination ART is recommended for all HIV-infected pregnant women regardless of CD4 count or HIV viral load. Decisions about ART are complex and should be made by the woman and her health care provider after discussing the risks and benefits. Clinicians are urged to consult an HIV specialist and the most current HHS recommendations when making therapeutic decisions. The Perinatal HIV Hotline (888-448-8765) provides free clinical consultation on all aspects of perinatal HIV care. The following discussion addresses some of the issues in determining ART

strategies and is taken from the HHS *Perinatal ARV Guidelines*.

The HHS Perinatal HIV Guidelines Working Group recommends fully suppressive combination ART for all pregnant women, unless there are compelling reasons based on pregnancy-specific maternal and fetal safety issues to modify this approach. Key recommendations from the HHS *Perinatal ARV Guidelines* include the following:

- Assess the woman's HIV disease status and make recommendations about initiating or altering an ARV regimen, as part of the initial evaluation.
- Recommend ARV prophylaxis to all pregnant women regardless of HIV viral load or CD4 count.
- Discuss known benefits and potential risks of ART.
- If HIV RNA level is >500-1,000 copies/mL, perform drug-resistance testing prior to starting or changing ART.
- If HIV is diagnosed late in pregnancy, ART should be initiated promptly without waiting for results of resistance testing.
- Emphasize the importance of adherence to the regimen.
- Ensure that the woman has access to and coordination of services among perinatal, primary care, and HIV providers as well as mental health and drug abuse services and income support as needed.
- Considerations about continuing ART after pregnancy are the same as for nonpregnant individuals.

A fundamental principle of the *Guidelines* is that therapies of known benefit should not be withheld during pregnancy unless they may cause adverse effects to the woman, fetus, or infant, and these adverse effects outweigh the potential benefits. Thus, women should be advised of the potential risks and benefits of ART (to the woman, fetus, and infant) and of the limited long-term data on outcomes for

infants with in utero exposure to ARVs, but treatment decisions should be guided by the woman's clinical, virologic, and immunologic status and by the goal of preventing perinatal transmission. An additional benefit of ART is the reduction in risk of transmission to sex partners. Women should be educated and counseled on the importance of close adherence to the ART regimen (see chapter *Adherence*).

Drug-resistance testing should be conducted for all pregnant women before the initiation of therapy, and for women who are already on ART without fully suppressed HIV RNA.

All women receiving ARVs during pregnancy for prophylaxis or for treatment should receive a combination containing at least three agents, with the aim of viral suppression to undetectable levels (i.e., <20-75 copies/mL, depending on the assay). Monotherapy (e.g., with ZDV) and dual therapy are not as effective and generally are not recommended. Current *Guidelines* recommend that the regimen include two nucleoside reverse transcriptase inhibitors (NRTIs) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). Regimen selection should be individualized on the basis of factors such as anticipated safety and efficacy, ARV history, results of resistance testing, and comorbidities (e.g., hepatitis B virus [HBV]) (see chapter *Antiretroviral Therapy* for considerations in selecting ARVs). It should be recognized that only limited information is available for many ARVs and ARV combinations regarding potential toxicities for the fetus or infant (see Table 5 of the *Guidelines*), and for dosage requirements with pregnant women.

The HHS *Perinatal ARV Guidelines* offer recommendations on the use of specific ARV agents during pregnancy. The table below shows "Preferred" and "Alternative" ARVs; others are classified as "Use in special circumstances" or "Insufficient data to recommend use." For more complete information, see Table 5 of the *Guidelines*.

Recommendations for ARV Use During Pregnancy

ARV Class	Preferred Agents	Alternative Agents
NRTI	<ul style="list-style-type: none"> Lamivudine Zidovudine 	<ul style="list-style-type: none"> Abacavir[#] Emtricitabine Tenofovir
NNRTI	<ul style="list-style-type: none"> Nevirapine* 	
PI	<ul style="list-style-type: none"> Atazanavir/ritonavir Lopinavir/ritonavir (Kaletra) 	<ul style="list-style-type: none"> Darunavir/ritonavir Saquinavir/ritonavir

* For women with CD4 counts of >250 cells/μL, NVP should be initiated only if benefit clearly outweighs risk, owing to the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 counts. Women who are already taking NVP at the start of pregnancy and are tolerating it well may continue NVP, regardless of CD4 count.

[#] Risk of hypersensitivity reaction; should be given only to patients who test negative for HLA-B*5701. Test for HLA-B*5701 before starting abacavir.

Adapted from U.S. Department of Health and Human Services. *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. Available at aidsinfo.nih.gov/guidelines. Accessed December 1, 2013.

The guidelines' preferred NRTI component is ZDV/3TC, because of data showing safety and efficacy in pregnancy. Alternative NRTIs listed above may be used for women with intolerance to ZDV (e.g., severe anemia) or documented resistance to ZDV (see "Safety and Toxicity of Antiretroviral Medications During Pregnancy," below). Tenofovir + 3TC or FTC is the preferred NRTI pair for women with hepatitis B coinfection (see "Special Circumstances," below).

Of the NNRTIs, NVP may be started for women with CD4 counts of ≤250 cells/μL or continued for women who are already on NVP-containing regimens. NVP generally should not be started for treatment-naive women with CD4 counts of >250 cells/μL because of an increased risk of symptomatic and potentially fatal hepatic and rash toxicity. Efavirenz is not recommended for use during the first 5-6 weeks of pregnancy because of concern for potential teratogenicity, but it can be continued in pregnant women already

taking an effective efavirenz-based regimen who present for antenatal care in the first trimester, and it can be considered for other women (after the first 6 weeks of pregnancy) if other agents are not appropriate (see “Safety and Toxicity of Antiretroviral Medications During Pregnancy,” below). There are insufficient pharmacokinetic and safety data to recommend the use of etravirine or rilpivirine during pregnancy.

Atazanavir + ritonavir and lopinavir/ritonavir are recommended PIs based on efficacy studies in adults and experience in pregnant women. For both of these (and for darunavir), serum levels may be low in the second and third trimesters; see the *Guidelines* for recommendations about dosage adjustments. The alternative PIs are ritonavir-boosted darunavir and ritonavir-boosted saquinavir, although pharmacokinetic data during pregnancy are limited. Nelfinavir has been used widely for pregnant women but current guidelines recommend its use only in “special circumstances” because, in nonpregnant adults, it has shown inferior efficacy compared with first-line agents. Indinavir also may be considered when preferred and alternative agents are not available. Fosamprenavir and tipranavir are not recommended because of lack of data in pregnancy, but they may be considered if other agents are not tolerated or are not appropriate.

The integrase inhibitor raltegravir may be considered if preferred or alternative agents are not appropriate. Pharmacokinetic and safety data in pregnancy are not sufficient to recommend the use of maraviroc or enfuvirtide, and they do not consider the newer agents rilpivirine, etravirine/cobicistat, or dolutegravir; these may be considered for use by women for whom drugs in other classes have failed but they should be prescribed in consultation with HIV and obstetric specialists.

ART Recommendations by Clinical Scenario

Recommendations for ARV Use by Pregnant Women

The HHS *Perinatal ARV Guidelines* offer recommendations on ART for pregnant women based on four clinical scenarios; these are categorized by the woman’s ART status when she presents for care (see Table 6 of the Guidelines). Note that current adult and adolescent guidelines recommend ART for all, regardless of CD4 cell count (see chapter *Antiretroviral Therapy*).

HIV-infected pregnant women currently receiving ART

Women already receiving ART should, in general, continue to receive it during pregnancy if it is suppressing viral replication. If the woman has detectable virus (e.g., >500-1,000 copies/mL) on therapy, HIV drug-resistance testing should be performed, and the regimen should be optimized to maximize the likelihood of achieving virologic suppression. Women presenting in the first trimester should be counseled about the risks and benefits of ART during this period. Discontinuation of therapy could lead to increased viral load and potential for transmission to the fetus.

Pregnant women receiving NVP-containing regimens should continue them, regardless of CD4 count, if they are virologically suppressed and tolerating the regimen. For women who become pregnant while taking efavirenz, current Guidelines state that, because the risk of neural tube defects is limited to the first 5 to 6 weeks of pregnancy and pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, efavirenz can be continued (assuming the regimen is maximally suppressive).

HIV-infected pregnant women who are ARV naive

All pregnant women should start potent combination ART. The drug regimen should be based on the recommendations of the *Perinatal ARV Guidelines* (see above and Table 5 of the Guidelines). As in other scenarios,

drug-resistance testing should guide ARV selection.

Starting ART early in pregnancy may be more effective in reducing perinatal HIV transmission but the potential benefits of early ART must be weighed against potential fetal effects of first-trimester exposure. Starting ART after the first trimester can be considered in women with high CD4 T-lymphocyte (CD4-cell) counts and low HIV RNA levels.

Inclusion of NRTIs with good placental passage (zidovudine, lamivudine, emtricitabine, tenofovir, or abacavir) is recommended.

ART should be continued intrapartum. ZDV should be administered to HIV-infected women by continuous IV infusion if they have HIV RNA levels of >400 copies/mL (or unknown HIV RNA levels) near delivery, regardless of ART regimen or mode of delivery.

After delivery, consider the indications for continuing ART and the woman's willingness and ability to do so (note that ART currently is recommended for all adults and adolescents); see "Postpartum Follow-Up of HIV-Infected Women," below, and chapter Antiretroviral Therapy.

HIV-infected pregnant women who previously have received ART or prophylaxis but are not currently receiving any ARV medications

In some instances, a pregnant woman has been on ART for her own treatment or for prophylaxis during a previous pregnancy and subsequently discontinued the medications. ARV drug-resistance testing should be conducted prior to initiating ART. The regimen should be chosen on the basis of previous ART experience and the reasons for stopping and results of past and current resistance testing, with avoidance of drugs and combinations with adverse maternal effects. The selection of an ART regimen for women with advanced HIV disease or a history of extensive prior therapy can be challenging, and consultation with an HIV specialist is

recommended. Principles of ARV selection are as described above.

For women who present late in pregnancy, ART should be started promptly, without waiting for results of resistance testing. The use of raltegravir during late pregnancy for women who have high viral loads has been suggested because of its ability to suppress viral load rapidly (an approximately 2- \log_{10} copies/mL decrease by week 2 of therapy). However, the efficacy and safety of this approach have not been evaluated and only anecdotal reports are available. Until more data become available on the safety of raltegravir use during pregnancy, this approach cannot be recommended for treatment-naive women.

Intrapartum ZDV infusion should be given as described above if the HIV viral load is >400 copies/mL near the time of delivery.

HIV-infected women who have received no ARV before labor and their Infants

HIV-infected pregnant women who have not received ARV prior to labor should be given ZDV as a continuous infusion during labor. The mother's need for continuing ARV treatment postpartum should be evaluated. Infants born to women who had no ART during pregnancy should begin ARV prophylaxis as close to birth as possible. In addition to receiving ZDV for 6 weeks, the infant should also be given three doses of NVP in the first week of life (at birth, 48 hours later, and 96 hours after the second dose).

Pharmacokinetic Considerations During Pregnancy

Physiologic changes that occur during pregnancy (e.g., prolonged gastrointestinal transit time; increase in body fat and water; and changes in cardiac, circulatory, hepatic, and renal function) may affect the kinetics of drug absorption, distribution, and elimination. Few pharmacokinetic studies have been conducted on levels of ARVs during pregnancy, but available data suggest that altered dosing for some PIs (e.g., atazanavir/ritonavir,

darunavir/ritonavir, lopinavir/ritonavir) may be required (see Table 5 of the *Guidelines*).

Special Circumstances

Hepatitis B Coinfection

Screening for HBV infection with hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs) is recommended for all pregnant women who have not been screened during the current pregnancy. The HBV vaccine series should be administered to pregnant women who screen negative for hepatitis B.

For pregnant women coinfecting with HIV and HBV, providers should treat both infections at once, by including a two-NRTI combination that is active against both infections. The NRTI combination tenofovir + 3TC or FTC is preferred for pregnant women with HIV/HBV, in combination with an NNRTI or PI. Liver transaminases should be monitored for signs of hepatotoxicity or HBV flare. Treatment may be complicated, and consultation with an expert is recommended. Also see the relevant discussion in the HHS *Perinatal ARV Guidelines*, and chapter *Hepatitis B Infection* in this manual.

HBV-infected pregnant women who are not immune to hepatitis A should be vaccinated. Infants born to coinfecting women should receive HBV immune globulin and start the HBV vaccine series within 12 hours after birth (with subsequent vaccine doses per usual protocol).

Hepatitis C Coinfection

Treatment for hepatitis C virus (HCV) is not recommended during pregnancy. Recommendations for ART during pregnancy are the same for women who are HIV/HCV coinfecting as for those without HCV coinfection. Liver transaminases should be monitored for signs of hepatotoxicity.

Coinfecting pregnant women should be tested for immunity to hepatitis A and HBV; if not

immune, they should be vaccinated. Infants born to coinfecting women should be evaluated for HCV infection.

See the relevant discussion in the HHS *Perinatal ARV Guidelines*, and chapter *Hepatitis C Infection* in this manual.

Safety and Toxicity of Antiretroviral Medications During Pregnancy

Limited data are available on the safety of ARVs during pregnancy, particularly when ARVs are used in combination. The existing safety and toxicity information is derived from animal and human studies, clinical trials, registry data, and anecdotal experience.

Several drugs are of special concern when used during pregnancy (see HHS *Perinatal ARV Guidelines*; Table 5), including the following:

- **Efavirenz:** Efavirenz is classified by the U.S. Food and Drug Administration (FDA) as a Pregnancy Class D drug because malformations have occurred in monkeys receiving efavirenz during the first trimester. Several cases of neural tube defects in humans after first-trimester exposure to efavirenz have been reported. As mentioned above, the *Guidelines* state that alternative ARVs should be strongly considered in women who are planning to become pregnant or are not using effective contraception with male partners. For pregnant women who present for antenatal care in the first trimester, discontinuation of efavirenz is not necessary, because the risk of neural tube defects is limited to the first 5-6 weeks of pregnancy and pregnancy is rarely recognized before 4-6 weeks.
- **Nevirapine:** Women, including pregnant women, who begin NVP therapy when their CD4 count is >250 cells/ μ L have nearly a 10 times higher incidence of hepatotoxicity than women initiated on NVP at lower CD4 counts. Symptoms of hepatotoxicity include fatigue, malaise, anorexia, nausea, jaundice, liver tenderness, and hepatomegaly. NVP should be initiated as part of an ARV

regimen for pregnant women with CD4 counts of >250 cells/ μ L only if the benefits clearly outweigh the risks (see Table 5 of the *Guidelines*). Women with higher CD4 cell counts who are already taking and tolerating NVP may continue it.

- **Didanosine + stavudine:** The combination of didanosine and stavudine may cause fatal lactic acidosis and hepatic steatosis and should be avoided unless no alternative is available. Patients may present with symptoms 1-6 weeks in duration that include nausea, vomiting, abdominal pain, dyspnea, and weakness; clinicians should be alert for early signs and symptoms of lactic acidosis and evaluate them promptly.

In addition, PIs have been associated with an increased risk of new-onset diabetes, worsening diabetes, and diabetic ketoacidosis. Of course, pregnancy itself is a risk factor for hyperglycemia. Clinicians should monitor the glucose levels of pregnant women taking PIs and should educate them about the symptoms of hyperglycemia. The HHS *Perinatal ARV Guidelines* recommend that pregnant women on ART should be screened with a standard 50 g glucose loading test at 24-28 weeks (see chapter *Care of HIV-Infected Pregnant Women*).

Information on ARV toxicity during pregnancy should be consulted carefully before treatment choices are made. The HHS *Guidelines* provide information on each ARV drug, including preclinical and clinical data, pharmacokinetic and toxicity data, and recommendations regarding use during pregnancy. These guidelines are updated routinely as information is received (see Table 5 and Appendix A of the *Guidelines*). Numerous other medications also are contraindicated for use during pregnancy, and potential toxicity should be considered carefully before any medication is given to a pregnant woman.

Adverse Events Related to ARV Drugs During Pregnancy

A number of studies have identified an increased risk (up to double) of preterm delivery in women who take combination therapy during pregnancy (whether started before or during pregnancy), while other studies have not. Given the conflicting data, the *Guidelines* advise clinicians to be aware of a possible small increased risk of preterm birth among women who receive ART. However, the benefit of ART for the mother's health and for prevention of perinatal transmission is clear, and combination ART should not be withheld. Until more is known, pregnant women who are taking combination regimens should be monitored closely for complications and toxicities and should be educated about the signs of premature labor.

Antiretroviral Pregnancy Registry

The Antiretroviral Pregnancy Registry collects observational data on HIV-infected pregnant women taking ARV medications to determine whether patterns of fetal or neonatal abnormalities occur. This is a project initiated by the pharmaceutical industry and overseen by an advisory committee comprising representatives from the CDC, National Institutes of Health, FDA, pediatric and obstetric providers, and others. Providers who care for pregnant women taking ARVs are encouraged to enroll patients in the registry at the time of initial evaluation. Information is confidential and patients' names are not used. More information can be obtained by visiting the registry website (www.apregistry.com/) or by calling 800-258-4263, 8:30 a.m. to 5:30 p.m. eastern time.

Intrapartum Management and Mode of Delivery

In 2012, a significant change was made in the *Guidelines* recommendation regarding intrapartum management of the woman with HIV infection. For women on ART with HIV

RNA levels of <400 copies/mL near delivery, IV ZDV during labor can be considered but is not required (though they should continue their usual ARV medications). IV ZDV is recommended for HIV-infected women with HIV RNA levels of ≥ 400 copies/mL (or with unknown viral loads) near delivery, regardless of antepartum regimen or mode of delivery. IV ZDV should be given to the woman during labor as a 1-hour loading dose of 2 mg/kg followed by a continuous infusion of 1 mg/kg per hour until delivery. Women on ART should continue their regimen on schedule as much as possible during labor, except that women receiving ZDV or a ZDV-containing fixed-dose combination whose viral load is ≥ 400 copies/mL should be given IV ZDV, with other components continued orally. For women on a stavudine-containing regimen, the stavudine component should be discontinued while IV ZDV is being administered.

For women on ART who have detectable viral load at the time of delivery, the addition of the single-dose NVP protocol (single dose to the woman during labor, single dose to the neonate) is not recommended in the United States, because clinical trials have not shown benefit and there is a risk of NVP resistance. For the neonate, an expanded infant prophylaxis regimen may be indicated (see “Follow-Up of HIV-Exposed Infants,” below).

Studies conducted before the availability of viral load testing found that cesarean delivery performed before the onset of labor or rupture of membranes significantly reduced the risk of perinatal transmission. However, in the United States and other settings where HIV-infected pregnant women typically receive potent combination ART, rates of HIV transmission are very low (<1%, unadjusted for mode of delivery) and it is difficult to determine whether delivery by cesarean section further decreases the risk of peripartum transmission.

For a woman with a viral load of <1,000 copies/mL, cesarean delivery is not routinely recommended; decisions on mode of delivery

should be individualized and based on discussions between the woman and her obstetric clinician. The woman and her health care providers should decide about mode of delivery before the onset of labor, based on her current viral load, her health status, and the outcome of discussions about other concerns, which should include counseling about the risks and benefits of cesarean delivery. If cesarean delivery is planned for standard obstetrical indications it should be scheduled for 39 weeks' gestation.

For a woman with HIV RNA levels of >1,000 copies/mL at or near the time of delivery, the HHS *Perinatal ARV Guidelines* and the American College of Obstetricians and Gynecologists recommend delivery by scheduled cesarean section at 38 weeks' gestation.

IV ZDV should be started 3 hours before a scheduled cesarean delivery. Prophylactic antibiotics are recommended at the time of cesarean delivery for HIV-infected women to decrease the risk of maternal infection.

It is not clear whether cesarean delivery provides any benefits in preventing perinatal HIV transmission once labor has begun or membranes are ruptured. Management of a woman for whom a scheduled cesarean was planned but who presents in labor or with ruptured membranes should be individualized on the basis of her HIV viral load, current ART regimen, length of time since membrane rupture, duration of labor, and other clinical factors.

The HHS *Perinatal ARV Guidelines* outline several scenarios in which the clinician must decide whether cesarean delivery is needed; see Table 8 of the *Guidelines* for further information. The data on the benefits of cesarean delivery are complex and must be considered alongside the increased risk to the mother after surgery. The clinician should consult an obstetric/HIV specialist to discuss specific situations.

A woman who presents in labor without a documented HIV status should receive an expedited HIV antibody test and, if the result is positive, should be presumed to be infected until the confirmatory HIV test result is received. She should receive IV ZDV immediately to prevent perinatal transmission, and her infant should start infant prophylaxis pending the mother's confirmatory results (see "Follow-Up of HIV-Exposed Infants," below). She will need confirmation and staging of her HIV infection (e.g., CD4 cell count, HIV RNA viral load) as well as referral to care for her own health and ongoing psychological support.

Questions remain about the management of labor when a vaginal delivery is planned. Because the duration of ruptured membranes is a risk factor for perinatal transmission, pregnant women with HIV infection should be counseled to go to a hospital for care at the first signs of labor or rupture of membranes. If the membranes rupture spontaneously before labor occurs or early in labor, the clinician should consider interventions to decrease the interval to delivery, such as administration of oxytocin. Procedures that potentially increase the neonate's exposure to maternal blood, such as the use of scalp electrodes or artificial rupture of membranes, should be avoided. Operative interventions with forceps or vacuum extractor and episiotomy should be performed only in select circumstances.

For management of postpartum hemorrhage owing to uterine atony, note that Methergine has significant interactions with PIs and with NNRTIs, and may interact with the pharmacokinetic booster cobicistat. Methergine should not be administered to women taking PIs, if possible. If alternative treatments are not available and Methergine must be used, it should be given at the lowest possible dosage and for the shortest possible duration. If Methergine is given to women taking NNRTIs, its dosage may need to be increased or additional uterotonic medications may be needed.

Postpartum Follow-Up of HIV-Infected Women

Women with HIV infection who have recently delivered need access to a comprehensive array of services for themselves and their infants. The clinician should refer the postpartum woman not only to her primary obstetric and HIV providers for family planning and HIV management but also to a pediatric HIV specialist for care of her infant. She should be referred as needed for mental health, substance abuse, and social support services. The clinician should be alert for indications of postpartum depression and should offer treatment promptly, if indicated. Adherence to ARV regimens may be particularly difficult for a woman in the immediate postpartum period because of postpartum physical and psychological changes and the demands of caring for a newborn; accordingly, the woman may require new or continued support services.

Women who are diagnosed through preliminary rapid HIV testing in labor will need thorough evaluation and management including confirmatory HIV testing and immediate linkage for medical and social services. They should not breast-feed unless the results of the confirmatory tests are received as negative.

Women should be evaluated regarding their ongoing need and desire for ART postpartum. Long-term ART generally should be recommended for all women, regardless of nadir CD4 count, in accordance with current HHS adult and adolescent guidelines. If ART was given only or primarily to reduce the risk of perinatal transmission, a discussion about continuing ART should include factors such as the woman's health status, her CD4 counts, the HIV status of her partner(s), and adherence issues. If the woman elects to discontinue ART postpartum, her need for treatment and willingness to restart ART should be reevaluated on an ongoing basis.

If ART is being discontinued, all drugs should be stopped at the same time if they have

similar half-lives. NNRTIs have longer half-lives than other agents, so an NNRTI should be discontinued for a period of time (the duration of this time has not been defined) before other ARVs, in order to avoid a period of NNRTI monotherapy and the development of NNRTI resistance mutations. Alternatively, a PI may be substituted for the NNRTI several weeks before stopping all the ARV agents. Note that, for women with HBV coinfection, discontinuation of NRTIs with anti-HBV activity (e.g., 3TC, emtricitabine, tenofovir) may result in a flare of HBV; consult with an expert before discontinuing ART.

Contraceptive counseling is an important aspect of postpartum care. Women should be offered dual-method contraception if pregnancy is not desired in the short-term future or if the ART regimen contains potentially teratogenic drugs such as efavirenz. Note that there are significant interactions between some hormonal contraceptives and PIs, NNRTIs, and elvitegravir/cobicistat. (See chapters *Care of HIV-Infected Pregnant Women* and *Health Care of HIV-Infected Women Through the Life Cycle*.)

Breast-feeding is not recommended in the United States or other parts of the world where replacement feeding is affordable, feasible, acceptable, sustainable, and safe. Women may experience culture-based and family pressure to breast-feed and may need support to use replacement feeding.

Follow-Up of HIV-Exposed Infants

The HIV-exposed neonate born to a mother with HIV infection should receive ZDV syrup at a dose based on the infant's gestational age. Infants at ≥ 35 weeks' gestation infant should be given ZDV syrup at a 4 mg/kg/dose PO BID, beginning as soon as possible after birth, preferably within 6-12 hours, and continuing for 6 weeks. Dosing for premature infants is detailed in the *Guidelines*. In the United States, the use of ARV drugs other than ZDV and NVP

cannot be recommended for premature infants because of lack of dosing and safety data.

Newborns should be discharged home with a supply of PO ZDV syrup. The use of ZDV for the neonate is recommended regardless of whether the mother has a history of resistance to ZDV. Two-drug therapy – specifically, ZDV by standard protocol for 6 weeks plus 3 doses of NVP given at birth, 48 hours later, and 96 hours after the second dose – is recommended for infants of mothers who did not receive ART before delivery or received ZDV only intrapartum. Few data are available to guide use of other combination therapies for neonates; consult with a pediatric HIV expert. Every HIV-exposed infant should be referred to a pediatric HIV specialist for diagnostic testing and monitoring of health status.

For an infant born to a mother whose HIV status is unknown, expedited HIV testing of the mother or the infant should be done as soon as possible. If the result for either is positive, ZDV prophylaxis for the infant should be started immediately. A confirmatory HIV test (e.g., Western blot) should be done at the same time and prophylaxis should be discontinued if the result is negative. If positive, the infant should be tested with an HIV DNA polymerase chain reaction (PCR) assay or an HIV RNA assay. If the newborn's HIV viral load test result is positive, prophylaxis should be discontinued and the infant should be referred urgently to a pediatric HIV specialist for management of HIV infection using combination ART.

Traditional HIV antibody testing cannot be used with infants because maternal antibodies may persist for up to 18 months. Diagnosis of HIV infection in infants requires virologic testing (HIV DNA or HIV RNA). Virologic testing should be performed by age 14-21 days, then at 1-2 months, and at 4-6 months. HIV can be diagnosed in an infant on the basis of two positive results from virologic tests done on separate blood samples at any time.

HIV can be excluded presumptively in an infant with two or more negative results from virologic tests, with one done at ≥ 14 days of age and one done at ≥ 1 month of age, or one negative virologic test result at ≥ 2 months of age, or one negative HIV antibody test result at ≥ 6 months of age. HIV can be excluded definitively with two or more negative virologic test results, with one test done at age ≥ 1 month and one done at ≥ 4 months. However, these tests may not be accurate in infants who are receiving combination ART. Some experts recommend retesting, using an antibody test, at age 12-18 months as a confirmatory test.

Infants should have a baseline complete blood count and differential and should be monitored for anemia while they are taking ZDV. Monitoring for anemia should be based on the infant's gestational age, ZDV dose, clinical condition, and maternal ARV history. Infants on ZDV/3TC prophylaxis should have a hemoglobin and neutrophil count at 4 weeks after initiation of ARVs.

Pneumocystis jiroveci pneumonia (PCP) prophylaxis for HIV-exposed infants is recommended starting at 6 weeks when the ZDV prophylaxis regimen is completed and continued until they are determined presumptively or definitively to be HIV seronegative. Initiation of PCP prophylaxis should be stopped or avoided altogether when HIV has been presumptively excluded.

Parents and family caregivers must be taught how to monitor the infant for signs of illness until an HIV diagnosis is made or ruled out. They also need to know that the infant's exposure to ARV agents in utero is an important part of the infant's medical history and should be shared with future health care providers. Although no enduring consequences of ARV exposure have been confirmed, the child may be at risk of long-term problems.

Patient Education

- The clinician should provide the pregnant woman with the most current information on the risk of perinatal HIV transmission and the importance of ARV prophylaxis.
- The clinician and the patient should have a detailed discussion about ART, both for the patient's own health and for decreasing the risk of perinatal transmission.
- The clinician should review with the patient the critical importance of her adherence to ART regimens before prescribing a regimen.
- The clinician should review possible adverse effects of the ARVs and give the patient specific instructions about managing them if they are mild or seeking medical advice if they are more serious, such as ongoing fatigue, persistent nausea and vomiting, or signs of hyperglycemia.
- The clinician should explain the signs and symptoms of early labor to the patient and emphasize the importance of seeking medical care if she has signs and symptoms of early labor or premature rupture of membranes.
- Early in the third trimester, the clinician and the patient should discuss the risks and potential benefits of cesarean section based on her viral load and clinical status.
- Intrapartum management, including the possible need to use intrapartum ZDV, should be discussed with the patient so that she knows to tell the delivery team about her HIV status when she presents in labor.
- The clinician should discuss infant feeding plans with the mother and reinforce that she should not breast-feed. The clinician may need to provide ongoing support for formula feeding.
- The clinician should advise HIV-infected mothers against pre-mastication of the infant's food and promote safer feeding options.

Care of HIV-Infected Pregnant Women

Background

This chapter describes the elements involved in caring for the pregnant woman with HIV infection, whether the woman was known to be HIV infected before conception or was found to be HIV infected during pregnancy. It is not intended to be a comprehensive discussion of this topic, and an HIV-experienced obstetrician and an HIV specialist should be involved in the management of all HIV-infected pregnant women. For centers that do not have HIV specialists available, experts at the National Perinatal HIV Consultation and Referral Service are available for consultation through the Perinatal HIV Hotline (888-448-8765).

The goals of HIV management during pregnancy are to maintain and support the woman's health, provide optimal antiretroviral treatment (ART) to preserve or restore her immune system and suppress viral replication, and to offer interventions that decrease the risk of perinatal HIV transmission. According to the U.S. Department of Health and Human Services perinatal guidelines, *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*, all HIV-infected pregnant women should be given ART during pregnancy to prevent mother-to-child transmission of HIV, and ART also is recommended for all women for their own health, regardless of pregnancy status (see chapter *Reducing Perinatal HIV Transmission*).

The first task in caring for an HIV-infected woman who is pregnant or considering pregnancy is to provide counseling that will allow her to make informed reproductive choices. Taking a careful reproductive history and providing preconception counseling should be part of any woman's routine primary care. To make informed choices about pregnancy, the patient needs education and information about the risk of perinatal transmission of HIV, potential complications of pregnancy, continuation or modification (or possibly, initiation) of ART, and the support she will need to optimize maternal and fetal outcomes. See chapter *Health Care of HIV-Infected Women Through the Life Cycle* for a more detailed discussion of preconception evaluation.

An appropriate ART regimen should be started before pregnancy to attain a stable, maximally suppressed maternal viral load prior to conception. This will support the woman's own health and greatly reduce the risk of HIV transmission either to a fetus or to a sex partner. Antiretroviral (ARV) resistance testing should be performed before ART is initiated. For women who intend to conceive, particular ARVs should be avoided, including those with increased risk of causing teratogenicity (e.g., efavirenz) or metabolic complications such as lactic acidosis (e.g., didanosine and stavudine). See chapter *Reducing Perinatal HIV Transmission*. It should be noted that most fetal organogenesis occurs in the early weeks of pregnancy, before most women know that they are pregnant. Thus, any medication with potential teratogenicity or fetal toxicity, whether an ARV or another drug, should not be administered to women who intend to become pregnant or may become pregnant. Certain medications (e.g., ribavirin) also should be avoided by male partners of women who may become pregnant.

Folate supplementation to reduce the risk of neural tube defects in the developing fetus should be started at least 1 month before conception, if possible, because the neural tube forms in the early weeks of pregnancy (see below).

Evaluation and Counseling of Pregnant Women

All HIV-infected pregnant women should receive thorough education and counseling about perinatal transmission risks, strategies to reduce those risks, and potential effects of HIV infection or HIV treatment on the course or outcomes of pregnancy.

- The goals of therapy for pregnant women receiving ART, as for all persons being treated for HIV infection, are to suppress the HIV viral load maximally (preferably to undetectable levels) for as long as possible, to improve quality of life, to restore or preserve immune function, and to prevent transmission to sexual (or injection drug equipment-sharing) partners. For pregnant women, an additional, and critical, goal is to reduce the risk of perinatal transmission as much as possible.
- Therapy-associated adverse effects, including hyperglycemia, anemia, and hepatic toxicity, may have a negative effect on maternal and fetal health outcomes. Pregnant women should be advised about possible ARV-related adverse effects and should be monitored regularly for these events.
- HIV-infected women should receive evaluation and appropriate prophylaxis for opportunistic infections (OIs), as well as the vaccinations indicated for persons with HIV infection (see below).
- Some medications, both ARVs and other drugs, may cause fetal anomalies or toxicity when taken during pregnancy. These should be avoided in pregnant women, unless the anticipated benefit outweighs the risk. Consult with an HIV or obstetric specialist, a pharmacist, or the drug labeling information before prescribing medications for pregnant women.
- Options for mode of delivery should be discussed early. The benefits and risks of vaginal vs. cesarean delivery are outlined in the perinatal guidelines. If the HIV viral

load is >1,000 copies/mL at 36 weeks of pregnancy, a scheduled cesarean delivery at 38 weeks' gestation is recommended to further reduce the risk of transmission.

Other evaluation and support measures for pregnant women should include the following:

- Screening for other potential maternal health problems, such as diabetes and hypertension
- Maternal nutritional evaluation and support, including initiation of a prenatal multivitamin containing folate (0.4 mg PO QD) to reduce the risk of fetal neural tube defects; for women receiving trimethoprim-sulfamethoxazole, some experts recommend higher folate doses in the first trimester; consult with an HIV-experienced obstetric specialist.
- Screening for psychiatric and neurologic disease
- Counseling about the risks of tobacco smoking; smoking cessation support as indicated (see chapter *Smoking Cessation*)
- Counseling about the risks of alcohol or drug use and support for discontinuation of these activities as needed
- Intimate partner violence screening
- Review of medications, including over-the-counter and nutritional agents, and discontinuation of medications with the potential for fetal harm
- Immunizations (e.g., influenza, Tdap, hepatitis B) as indicated
- Institution of the standard measures for evaluation and management (e.g., assessment of reproductive and familial genetic history, screening for infectious diseases or sexually transmitted diseases [STDs])
- Planning for maternal-fetal medicine consultation, if desired or indicated
- Selection of effective and appropriate postpartum contraceptive methods, if desired

Comprehensive Care of Pregnant Women with HIV Infection

Comprehensive care is important for pregnant women with HIV infection to achieve a healthy pregnancy and delivery. A multidisciplinary approach is the most effective way to address the medical, psychological, social, and practical challenges. For example, while her medical care is being managed by her obstetrician and an HIV specialist, the pregnant woman may need help from a social worker to find appropriate social services for food, housing, child care, and parenting issues. The pregnant woman may need counseling and psychological support for herself and her partner, as well as referrals for substance abuse and detoxification programs. Peer counselors may be of particular assistance. Some patients may need legal or domestic violence services during and after pregnancy. Cooperation and communication between the obstetrician or nurse/midwife and the primary HIV provider are imperative throughout the pregnancy and early postpartum period. Referral to a maternal-fetal medicine specialist may be needed in complicated obstetric cases.

Prenatal Care

All pregnancy-related complications seen in HIV-uninfected women, such as hypertensive disorders, ectopic pregnancy, psychiatric illness, multiple gestation, preterm delivery, and STDs, also can occur in HIV-infected women. These problems must be recognized quickly and treated appropriately to avoid life-threatening complications. Ideally, HIV-infected pregnant women are managed by both an experienced obstetrician-gynecologist and an HIV specialist. Communication between these specialists about medications, expectations, and complications is vital for the health and well-being of both mother and baby. If complications occur or abnormalities are detected, they should be evaluated and treated as indicated by the condition, and referral should be made to a maternal-fetal medicine specialist, if possible. Antenatal fetal surveillance and testing to identify fetal abnormalities should be carried out using guidelines established by the American College of Obstetricians and Gynecologists.

The suggested testing and monitoring practices for pregnant women with HIV infection, from the first trimester to labor and delivery, are presented in Tables 1 and 2.

Table 1. Recommended Evaluation and Routine Monitoring of the Pregnant Woman with HIV Infection

Evaluation		Frequency
History		
HIV History	Date of diagnosis	Initial
	Signs and symptoms	Initial and at every visit
	Nadir CD4 and current CD4 cell count; HIV viral load	Initial
	ARV history, including regimen efficacy, toxicity, and ARV resistance	Initial
	Opportunistic infections and malignancies	Initial and at every visit
	History of STDs	Initial
	Adherence	Initial and at every visit
Obstetric History	Number of pregnancies; complications and outcomes (GPAL [gravida, para, abortion, living children]); mode of deliveries	Initial
	History of genetic disorders	Initial
	Use of ARV prophylaxis during previous pregnancies	Initial
	HIV status of children	Initial
Current Pregnancy	Last menstrual period (LMP)	Initial
	Pregnancy: intended or not	Initial
	Contraceptive methods used, if any	Initial
	Gestational age (can be calculated in a woman with regular menses by counting weeks from LMP)	Initial and at every visit
	Estimated date of delivery	Initial
	Signs or symptoms of maternal complications: elevated blood pressure, headache, significant edema, gastrointestinal or genitourinary symptoms, vaginal discharge or bleeding, decreased fetal movement (fetal movement is usually first detected at 18-24 weeks of pregnancy)	Initial and at every visit
	Screen for depression	Initial
	Screen for intimate-partner violence	Initial and at every visit

Evaluation		Frequency
Physical Examination		
General	Vital signs and weight	Initial and at every visit
	Funduscopy, breast examination	Initial and as indicated
Gynecologic/ Obstetric (usually performed by the obstetric provider)	Pelvic examination, STD screening, examination for perineal or vaginal lesions (discoloration, condyloma, ulcerative lesions, vaginal discharge), cervical lesions, discharge or bleeding	Initial and as indicated
	Fundal height, correlating with gestational age (concordant between 18 and 30 weeks)	Every visit starting the second trimester
	Fetal heart beat and rate: may be audible with Doppler devices as early as 12 weeks	Initial and at every visit
	Fetal movements and position in third trimester	Every visit starting at 24 weeks
Laboratory and Other Studies		
HIV	HIV antibody test (if not already documented)	Initial
	HIV viral load and CD4 count (total and percentage); results obtained at 35-36 weeks guide decisions on the mode of delivery	Viral load at initial visit, 2-4 weeks after starting or changing ART, every 4 weeks until undetectable, then at least every 3 months CD4 count at initial visit and at least every 3 months
	Genotype if ARV naive or detectable HIV RNA while on ART	Initial and as indicated
	Cytomegalovirus (CMV) immunoglobulin G (IgG)	Initial
	<i>Toxoplasma</i> IgG	Initial
	G6PD level in appropriate ethnic or racial groups if PCP prophylaxis with dapsone is anticipated	Initial
General	Complete blood count (CBC)	Initial and every 3 months or more frequently, based on ARV regimen or symptoms; check weeks 24-28
	Chemistries, liver enzymes (LFTs)	Initial and every 3 months or more frequently, based on ARV regimen or symptoms If on NRTIs, monitor electrolytes and hepatic enzymes monthly in third trimester
	Fasting lipids and glucose	Initial and as indicated
	Blood group	Indicated
	Rh antibody screen	Indicated

	Evaluation	Frequency
Pregnancy Specific	Ultrasound	First trimester: confirm gestational age and potential timing for cesarean delivery if necessary Second trimester: assess fetal anatomy for women on combination ART during first trimester
	Screening for chromosomal abnormalities	Screen for neural tube and abdominal wall defect, trisomy 21, and trisomy 18; first-trimester testing may include laboratory and ultrasound exam, whereas patients in their second trimester are evaluated by multiple marker screening Abnormal result requires further investigation – consider amniocentesis only if abnormality is detected on multiple marker screening or level-2 sonogram and the woman is on suppressive ART (to decrease risk of HIV transmission); voluntary and requires counseling
	Diabetes screening	Consider at 20 weeks; check glucose 1 hour after 50 g glucose load; perform 3-hour glucose tolerance test if screen is abnormal If 3-hour test result is abnormal, perform regular glucose monitoring, especially in women taking protease inhibitors (PIs)
	Rubella antibody	Initial
	Varicella IgG for those without history of chickenpox or shingles	Initial
	Screening for syphilis: rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL)	Initial and during weeks 32-36
	Consider bacterial vaginosis (BV) screening (BV increases risk of preterm labor)	Week 24-28
	Screening for streptococcus B (if result is positive, intrapartum chemoprophylaxis is indicated)	Week 32-36
	Screening with herpes simplex virus-2 serology in high-risk patients is recommended by some experts	Initial
	Urinalysis and clean-catch urine culture	Initial and as indicated
Papanicolaou test	Initial and as indicated (colposcopy is done on pregnant women, but biopsy is avoided; management resumes postpartum, after the 6-week postpartum visit)	

	Evaluation	Frequency
Hepatitis Serologies	Hepatitis A virus (HAV) antibody (IgG)	Initial
	Hepatitis B virus (HBV): HBsAg, HBcAb , HBsAb	Initial
	Hepatitis C virus (HCV) antibody	Initial
TB Screening	Tuberculin skin test (purified protein derivative [PPD]), more reliable if CD4 count is >200 cells/ μ L (induration >5 mm is positive); or interferon-gamma release assay (IGRA); note there is limited experience with IGRAs in pregnant women	Initial
Disease Specific	Consider hemoglobin electrophoresis, if anemic or at increased risk of hemoglobinopathies	Initial
	Serum screening for Tay-Sachs disease – both partners – if at increased risk	Initial
	Urine toxicology screen	Initial and as indicated

Table 2. Recommended Evaluation and Routine Monitoring of the Pregnant Woman with HIV Infection: Labor and Delivery

Test	Comment
Record Review	<ul style="list-style-type: none"> Documentation of HIV serostatus, blood type and Rh, hepatitis serologies, RPR Review of ART, if any, during pregnancy Review of HIV viral load results during pregnancy
Physical Evaluation	<ul style="list-style-type: none"> Vital signs and fetal heart rate Frequency and intensity of contractions Fetal lie, presentation, attitude, and position Vaginal examination: rule out HSV lesions; detect ruptured membranes; determine cervical effacement, dilatation, and position Avoid procedures that increase risk of perinatal HIV transmission (e.g., fetal scalp electrodes, scalp sampling, or assisted rupture of membranes)
Admission Laboratory Tests	<ul style="list-style-type: none"> Complete blood count Liver function tests RPR or VDRL, if not done recently Repeat hepatitis B and C testing, if at risk of acquisition of hepatitis B or C, to prevent perinatal transmission of these infections Others, as required by specific state laws

Immunizations and Opportunistic Infection Prophylaxis

Immunizations During Pregnancy

Generally, immunizations should be given before pregnancy, if possible. However, immunizations should be considered during pregnancy when the risk of exposure to an infection is high, the risk of infection to the mother or fetus is high, and the vaccine is unlikely to cause harm. The inactivated influenza virus and Tdap vaccines both meet this criteria and are generally recommended during pregnancy, as are certain others (see Table 3). Some vaccinations (particularly live-

virus vaccines such as measles/mumps/rubella and varicella vaccines) are contraindicated, and others should be given only if the anticipated benefit of the vaccination outweighs the risk. Special considerations for immunizations in HIV-infected individuals are discussed in chapter *Immunizations for HIV-Infected Adults and Adolescents*.

Because vaccinations may cause a transient increase in the HIV viral load and theoretically may increase the risk of perinatal HIV transmission, vaccination should be given after pregnant women are on ART.

Table 3. Immunizations and Postexposure Prophylaxis in Pregnant Women with HIV Infection

Immunization	Comment
Hepatitis A virus (HAV)	Recommended for susceptible patients at risk of becoming infected, those with chronic HBV or HCV, those traveling to endemic areas, injection drug users, and those in the setting of a community outbreak.
Hepatitis B virus (HBV)	Generally recommended for susceptible patients at risk of HBV infection during pregnancy.
Human Papilloma Virus (HPV)	Not recommended during pregnancy.
Influenza	Inactivated influenza vaccine is recommended for all pregnant women, before or during flu season. Live attenuated vaccines should not be used.
Measles/Mumps/Rubella (MMR)	Contraindicated.
Pneumococcus	Generally recommended. Limited data on safety during pregnancy for both the PPSV23 and PCV13 vaccines: no reports of adverse effects with PPSV23; limited experience with PCV13.
Tetanus-diphtheria-pertussis (Tdap)	Recommended during each pregnancy. Can be given at any time in pregnancy, but optimally between 27 and 36 weeks' gestation (to maximize maternal antibody response and passive antibody transfer to the infant). In addition, family members and caregivers should receive Tdap vaccination.
Varicella <ul style="list-style-type: none"> • Primary vaccination • Zoster vaccination 	Contraindicated

Immunization	Comment
Immune globulins (for postexposure prophylaxis in susceptible individuals)	
Measles	Recommended after measles exposure.
Hepatitis A	Recommended after exposure (close contact or sex partner), or in case of travel to endemic areas.
Varicella-zoster virus immune globulin (VariZIG)	Recommended for susceptible individuals after close contact with someone with varicella or herpes zoster (give as soon as possible, and within 10 days of exposure).
Hepatitis B immune globulin (HBIG)	Recommended for susceptible individuals after needlestick or sexual exposure to a person with hepatitis B infection.

Opportunistic Infection Prophylaxis

Some OIs can have an adverse effect on pregnancy. In turn, pregnancy can affect the natural history, presentation, treatment, and significance of some OIs. Women should be monitored carefully for OIs during pregnancy, with special attention given to nonspecific symptoms such as fatigue, back pain, and weight loss, which may be attributable to HIV-related illness rather than to pregnancy. Respiratory symptoms in particular merit rapid, aggressive investigation. Clinicians should follow the most current recommendations of the U.S. Centers for Disease Control and Prevention (CDC), National Institutes of Health, and Infectious Diseases Society of America, *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*, which give special consideration to pregnant women for each OI discussed. The indications and recommendations for OI prophylaxis generally should follow the guidelines for adults (see chapter *Opportunistic Infection Prophylaxis*). However, because of the risks of teratogenicity or harm to the developing fetus, some drugs routinely used for prophylaxis of OIs in nonpregnant adults are contraindicated during the first trimester of pregnancy, whereas others should not be used at any time during pregnancy.

Special Considerations for OI Prophylaxis During Pregnancy

Trimethoprim-sulfamethoxazole use

In pregnant women, folate deficiency increases the risk of neural tube defects in the developing fetus. Trimethoprim inhibits the synthesis of metabolically active folic acid and thus increases the risk of folate deficiency and congenital anomalies.

Pregnant women, or women who may become pregnant, who are taking trimethoprim-sulfamethoxazole (TMP-SMX, Septra, Bactrim, cotrimoxazole) should be given folate supplementation to reduce the risk of neural tube defects. However, folate also counteracts the activity of TMP, and may compromise the therapeutic efficacy of TMP-SMX.

The recommended dosage of folic acid usually is 0.4 mg/day, but the optimal dosage in women on TMP-SMX is not clear. Some experts recommend higher dosages during the first trimester, when the fetus is at greatest risk for teratogenic effect.

TMP-SMX is the recommended drug for women who require prophylaxis against PCP during pregnancy; alternatives to TPM-SMX during first trimester include aerosolized pentamidine and atovaquone.

Genital herpes

Women with HIV infection are more likely than HIV-uninfected women to experience outbreaks of genital herpes. If HSV is transmitted to the infant, neonatal infection can be severe, even if it is detected and treated early. In addition, there is increased genital shedding of HIV in those with active genital HSV lesions though it is not known whether this remains true in women treated with effective ART. Some experts recommend obtaining HSV-2 serologies in a woman whose clinical history is unclear. Treatment for symptomatic HSV infections should be offered during pregnancy, and suppressive therapy should be given to women with frequent recurrences. Suppressive therapy with acyclovir or valacyclovir also should be offered to any woman with an HSV recurrence during pregnancy, starting at 36 weeks' gestation. If a woman has an active outbreak of genital HSV or experiences prodromal symptoms at the time of labor or membrane rupture, delivery by cesarean section is indicated. Prophylaxis for pregnant women who are seropositive for HSV-2 but who do not have a history of genital lesions is not recommended.

Tuberculosis

Prophylaxis is recommended for any woman with a positive PPD skin test result (≥ 5 mm induration), a positive IGRA result, or a history of exposure to someone with active tuberculosis, after active disease has been ruled out. Patients receiving isoniazid also should receive pyridoxine to reduce the risk of neurotoxicity.

Toxoplasmosis

All HIV-infected persons should be tested for IgG antibodies to *Toxoplasma* soon after HIV diagnosis, and this should be a part of antenatal testing for pregnant women with HIV infection. Women with a negative IgG titer should be counseled to avoid exposure to *Toxoplasma* (e.g., by avoiding raw or undercooked meats, unwashed or uncooked

vegetables, and cat feces). Women with previous exposure to *Toxoplasma* (positive IgG titer) should be given prophylaxis during pregnancy, if the CD4 count is <100 cells/ μ L. For women who require prophylaxis, TMP-SMX is the preferred agent (see considerations for TMP-SMX, above).

HIV-infected pregnant women who have evidence of primary or reactivated *Toxoplasma* infection should be managed by a specialist.

Antiretroviral Therapy

The current HHS guidelines recommend treating HIV infection in all pregnant women, using the same principles and modalities as used for nonpregnant individuals. HIV-infected pregnant women should receive potent combination ART regimens comprising at least three ARVs. The choice of ARV regimen should be based on what is likely to be optimal for the woman's health, the potential effect on the fetus and infant, resistance test results, the woman's previous experience, if any, with ART, and her stage of pregnancy. ARV resistance testing should be performed before initiating or changing therapy, but should not delay the initiation of ART in late stages of pregnancy. Combination ART in pregnancy should include ZDV or another NRTI with good placental passage. ARV agents with potential teratogenic effects should be avoided in the early weeks of pregnancy (however, efavirenz may be continued during pregnancy, provided the regimen is tolerated and is providing effective virologic control). Women who have very high CD4 cell counts and are taking ART only for the prevention of perinatal transmission may delay initiation of therapy until after the first trimester, though effectiveness in preventing transmission may be decreased. For women already taking ART at the time they become pregnant, the regimen should be reevaluated for its appropriateness during pregnancy to avoid potentially toxic medications and to ensure maximal virologic

suppression. Generally, any ART regimen that is effective and tolerated by the woman may be continued during pregnancy. If necessary, the ART regimen may be changed but therapy should continue without interruption.

Discontinuation of ART could lead to an increase in viral load, which could result in a decline in immune status and an acceleration of disease progression, thereby increasing the risk of HIV transmission to the fetus.

For further information about ART during pregnancy, see chapter *Reducing Perinatal HIV Transmission* and the HHS *Perinatal ARV Guidelines*. The guidelines include recommendations regarding ARV regimens, modes of delivery (vaginal vs. cesarean section), and potential adverse events, as well as a detailed discussion of individual ARV agents. Additionally, the treatment of pregnant women with HIV/HBV coinfection and HIV/HCV coinfection is discussed.

Antiretroviral Pregnancy Registry

To improve tracking of pregnancy-related adverse events and fetal effects, an Antiretroviral Pregnancy Registry has been established as a collaborative project among the pharmaceutical industry, pediatric and obstetric providers, the CDC, and the National Institutes of Health. The registry collects observational data on HIV-infected pregnant women taking ARV medications to determine whether patterns of fetal or neonatal abnormalities occur. Pregnant women taking ARVs can be placed in this confidential follow-up study by calling 800-258-4263, 8:30 a.m. to 5:30 p.m. eastern time; the fax number is 800-800-1052. Information is confidential and patients' names are not used. Providers are encouraged to add to the available information on fetal risk by using this registry at first contact with a pregnant woman receiving ART. More information can be obtained at www.APRegistry.com.

Pregnancy-Specific Complications and Management

Nutrition risk and inadequate weight gain

Maternal nutrition and weight must be monitored throughout the pregnancy. A food diary may be a useful tool in assessing intake, and nutritional counseling is recommended.

Nausea and vomiting

Women with signs of dehydration should be assessed and treated appropriately in collaboration with the obstetrician or nurse/midwife. Any medication used for nausea and vomiting must be assessed for drug-drug interactions with all HIV-related medications the patient is taking.

Hyperglycemia

Pregnancy is a risk factor for hyperglycemia, and women treated with PIs may have an even higher risk of glucose intolerance than other pregnant women and must be monitored carefully. New-onset hyperglycemia and diabetes mellitus, and exacerbation of existing diabetes, all have been reported in patients taking PIs. Clinicians should educate women taking PIs about the symptoms of hyperglycemia and closely monitor glucose levels. Women with HIV-infection should receive standard glucose screening at 24-28 weeks' gestation. Women who were taking a PI-based regimen prior to pregnancy may be screened earlier according to recommendations for women at high risk of glucose intolerance. The newborn should be checked for neonatal hypoglycemia at 1 and 4 hours after birth.

Lactic acidosis

Lactic acidosis is a rare but life-threatening complication that has been reported in pregnant women taking nucleoside reverse transcriptase inhibitors, particularly didanosine and stavudine. The combination of didanosine and stavudine should be avoided during pregnancy. Clinical suspicion

of lactic acidosis should be prompted by vague symptoms such as malaise, nausea, or abdominal discomfort or pain.

Hyperbilirubinemia

Women taking atazanavir or indinavir frequently develop elevated indirect bilirubin, but it is not known whether treatment during pregnancy exacerbates physiologic hyperbilirubinemia in newborns. Women who are taking indinavir may have an increased risk of nephrolithiasis, but evidence of harm to their newborns has not been demonstrated. Indinavir should be used during pregnancy only when preferred and alternative agents are not acceptable, and it must be boosted with low-dose ritonavir.

Pain management

Pain management during labor and delivery may be complicated by drug interactions with ARV agents and by the higher medication tolerance in women who have addictions. Additional pain medication may be needed for women with histories of drug use.

Invasive perinatal procedures

The risk of HIV transmission to the fetus during invasive procedures (e.g., amniocentesis, chorionic villus sampling, and percutaneous or umbilical cord blood sampling) must be weighed carefully against the possible benefits of these procedures. Current HHS guidelines suggest that women undergoing such procedures should be on effective ART, preferably with undetectable HIV RNA. The use of fetal scalp electrodes and artificial rupture of membranes should be avoided if possible, and forceps or vacuum extractors and episiotomy should be used only if there are clear obstetric indications.

Postpartum considerations

Because HIV can be transmitted to the infant through breast-feeding, breast-feeding is contraindicated in the United States and other resource-adequate countries where safe

replacement feeding is available. Breast-feeding information should be removed from patient educational material pertaining to labor and delivery. Lactation suppression techniques can be used as needed to reduce lactation discomfort. Clinicians should recognize that women in some cultural groups are expected to breast-feed and they may need additional support to use formula rather than breast-feed.

ART should be continued, unless the woman refuses ARVs. Maternal and infant medication adherence must be discussed with the new mother. Adherence barriers for the mother during the postpartum period may be different from those during pregnancy (e.g., because of changes in daily routine, sleep/wake cycles, and meals).

New mothers should be observed carefully for signs of bleeding or infection.

If the mother's glucose tolerance test result was abnormal during pregnancy, she should be reevaluated 6-12 weeks postpartum and should be screened yearly for diabetes.

At the infant's 2-week follow-up visit, the HIV pediatric clinician should address the mother's concerns, screen for postpartum depression, assess adherence to her own and the infant's ARV medications, and ensure follow-up for the 6-week postpartum visit with the obstetric provider and soon thereafter with the primary HIV care provider. These visits provide an opportunity to address the woman's contraceptive needs and options, if this was not done previously (see chapter *Health Care of HIV-Infected Women Through the Life Cycle*).

Contraception

Many contraceptive choices are available for HIV-infected women; considerations are discussed in chapter *Health Care of HIV-Infected Women Through the Life Cycle*. Consistent condom use should be emphasized, and for women who wish to avoid pregnancy a "dual-protection" strategy, condom use plus another method of birth control, should be

emphasized. This strategy effectively prevents pregnancy, prevents transmission of HIV to sex partners, and prevents the acquisition of sexually transmitted diseases. It is important to provide women with all contraceptive options including long-acting reversible contraceptive methods such as the intrauterine device and implants.

Patient Education

- Reinforce regularly and clearly the notion that, when the mother cares for herself, she is caring for her infant. Talk with the patient about stress, the importance of adequate mild-to-moderate exercise, and sufficient rest.
- Emphasize that regular prenatal care is extremely important to prevent complications of pregnancy.
- Use of a prenatal vitamin supplement is important, but cannot replace healthy food intake. Develop a plan with the patient for attaining the desired weight gain during pregnancy, while maintaining a healthy nutritional intake.
- Cigarette, alcohol, and drug use contribute to poor maternal nutrition and can harm the developing fetus. Illicit drug use increases the risk of transmitting HIV to the infant. Injection drug use can transmit HBV, HCV, and CMV to the mother and to the baby. Encourage cessation of cigarette, alcohol, and drug use, and offer referrals for treatment, as needed.
- Be sure the woman understands all planned procedures and treatments and understands their potential risks and benefits both to herself and to the fetus.
- Discuss the risks and benefits (to the woman and fetus) of each medication to be taken during pregnancy, including those for which there are limited data on teratogenicity.
- Discuss ART as a benefit to the woman's health and as part of the strategy to reduce

the risk of perinatal HIV transmission to the fetus or newborn. Also discuss the effect of ART on reducing risk of HIV transmission to sex partners.

- For women at risk, diligent use of “safer sex” during pregnancy is important for preventing infection with STDs and CMV, which can cause more complications when HIV is present. STDs can harm fetal development and may increase the risk of HIV transmission to the baby. New genital herpes infections during pregnancy can cause severe complications and even death in neonates.
- For women with negative *Toxoplasma* titers, explain the need to avoid undercooked meat, soil, and cat feces.
- Teach the pregnant woman how to obtain medical attention quickly at the first signs of OI or other complication. Discuss what to watch for and how to get help when emergencies arise in the evenings or on weekends or holidays.
- Help the patient clarify her child care options and support systems for raising a family.

Health Care of HIV-Infected Women Through the Life Cycle

Background

Women with HIV infection have the same reproductive and life cycle health needs and concerns as women without HIV infection. However, for women with HIV infection, certain gynecologic problems may be more common or more frequent. In addition, issues regarding antiretroviral therapy (ART), contraception, and preconception counseling require special attention. This chapter addresses some of the unique health care needs of HIV-infected women across the lifespan, from menarche through postmenopause, and describes the essential elements of care. For further information, see chapters *Reducing Perinatal HIV Transmission*, *Care of HIV-Infected Pregnant Women*, and *Antiretroviral Medications and Hormonal Contraceptive Agents*.

Epidemiology and Factors Affecting HIV Transmission

Heterosexual transmission of HIV is more efficient from man to woman than from woman to man. Transmission can occur through intact vaginal tissue; no damage to the vaginal lining is required. Women have specific risks of HIV acquisition at different phases of the lifespan:

- Young adolescents have immature genital tracts and increased cervical ectopy (increased vulnerability to HIV and other sexually transmitted diseases [STDs])
- Women of reproductive age may desire pregnancy and childbearing (potentially increasing risky sexual behaviors)
- Married or partnered women may be monogamous with male partners who have risk factors for HIV infection (women may lack awareness of partner's risk behaviors)
- Postmenopausal or posthysterectomy women may have vaginal atrophy (decreasing the anatomic barrier to HIV), or may have no fear of pregnancy or have a perception that they are at low risk of infection (increasing risky sexual behaviors)
- Additionally, woman-to-woman transmission may occur if risk factors are present

Psychosocial/Emotional Factors Unique to Women

Women may inherit social roles and responsibilities as caretakers for extended family members and often for friends, and may not give sufficient priority to their own medical care. Furthermore, heterosexual women frequently are faced with unequal power and socioeconomic relationships with their male partners. These women may be more likely to exchange sex for money, less likely to successfully negotiate protected sex, and less likely to leave a relationship they perceive as risky. They may be fearful about disclosing their HIV status.

Sexual abuse appears to increase the risk of HIV transmission to HIV-uninfected women. For HIV-infected women, intimate partner violence and sexual coercion appear to occur at about the same rates as for HIV-uninfected women (>60% in one review). However, HIV-infected women appear to be subjected to more frequent and more severe abuse. HIV-infected women should be screened for intimate partner violence and referred to intervention services, if indicated. The U.S. Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force recommend several screening tools (see "References," below). The Abuse Assessment Screen (AAS) is one tool recommended by the

CDC. It originally was intended for screening pregnant women but has since been used more widely.

Abuse Assessment Screen

- Have you ever been emotionally or physically abused by your partner or someone important to you?
- Within the last year, have you been hit, slapped, kicked, or otherwise physically hurt by someone? If yes, by whom? How many times?
- Since you have been pregnant, have you been hit, slapped, kicked, or otherwise physically hurt by someone? If yes, by whom? How many times and where?
- In the last year, has anyone forced you to have sexual activities? If so, whom? How many times?
- Are you afraid of your partner or anyone you listed above?

ART Issues Particular to Women

In general, women on ART have virologic and immunologic responses comparable to those of men; however, several studies have shown that women discontinue ART more frequently than men. Women have higher rates of adverse effects from a number of antiretroviral (ARV) medications, in part because serum levels of at least some ARVs are higher in women. Pregnancy may require changes in ART, either because of pharmacokinetic changes or because of toxicity. See Table 1.

Table 1: Special Considerations for Use of Antiretrovirals with Women

ARV Issues for Women	Considerations
ARV adverse effects	<p>Some ARV adverse effects may be more severe in women:</p> <ul style="list-style-type: none"> • Abacavir hypersensitivity • Anemia (zidovudine) • Bone loss, especially after menopause • Hepatotoxicity (nevirapine) • Lactic acidosis (particularly with stavudine + didanosine) • Lipoaccumulation: central fat accumulation in breasts, abdomen; lipoatrophy: face • Neuropathy (stavudine, didanosine) • Severe rash (nucleoside reverse transcriptase inhibitors [NNRTIs], darunavir, tipranavir)
Pregnancy	<p>Teratogenicity:</p> <ul style="list-style-type: none"> • Efavirenz (EFV) is associated with neural tube defects in primates with in utero exposure. Consider alternatives, if feasible, in women who 1) are planning to become pregnant or 2) are sexually active with male partners and not using effective contraception. In women who become pregnant while taking EFV, EFV may be continued because the risk of neural tube defects is restricted to the first 5-6 weeks of pregnancy and pregnancy is rarely recognized before 4-6 weeks of pregnancy. Efavirenz is classified by the U.S. Food and Drug Administration (FDA) as a Pregnancy Category D drug. <p>Pharmacokinetic (PK) changes:</p> <ul style="list-style-type: none"> • Serum levels of some ARVs may be decreased during pregnancy (e.g., unboosted protease inhibitors [PIs], and boosted PIs including atazanavir/ritonavir, darunavir/ritonavir, and lopinavir/ritonavir). • Some ARVs should be avoided and certain ARVs may require dosage adjustment in the third trimester. • PK studies in pregnancy are not available for some ARVs. <p>See chapter <i>Reducing Perinatal HIV Transmission</i></p>
Contraception	<p>There are significant interactions between some hormonal contraceptive agents and certain ARVs; see "Contraception," below.</p>

Baseline Reproductive History

Taking a careful reproductive history should be a part of routine primary care for any woman. Important information to gather includes the following:

- Age of menarche
- Menstrual history: last menstrual period (LMP), amenorrhea, menstrual irregularity, uterine fibroids, endometriosis
- Obstetrical history: G-P-A-L
- G (gravida, or number of pregnancies), P (parity, or number of births), A (abortion; number of miscarriages or terminations), L (number of living children)
 - Pregnancy complications and outcomes: full-term, premature births, mode of deliveries
 - Use of ART during pregnancy
 - HIV status of children
- Sexual activity: vaginal, oral, anal; condom use; number of partners; sex of partners; HIV status of partners
- Plans and desires for childbearing
- Contraception, past and current
- Date of last Papanicolaou (Pap) test and results; history of abnormal Pap test results
- Gynecologic procedures: colposcopy/biopsy, loop electrosurgical excision procedure (LEEP), cervical surgery, tubal ligation, partial or total hysterectomy; and indication for these

- History of STDs, bacterial vaginosis, vulvovaginal candidiasis, herpes, warts; especially recurrence
- Current symptoms: vaginal discharge, vulvar/vaginal/anal pain, dysuria, dyspareunia (pain with intercourse), lesions, intermenstrual bleeding, postcoital bleeding

Elements of Gynecological Care

Women with HIV infection should receive routine screening for gynecologic cancers and infections. The incidence, prevalence, and persistence of human papillomavirus (HPV) infection and cervical, vaginal, vulvar, and anal dysplasia are more common in women with HIV infection, especially among women with low CD4 counts. It is not clear that initiation of suppressive ART improves clinical outcomes of women with dysplasia (see chapter *Cervical Dysplasia*). Other common gynecological problems include recurrent yeast vaginitis, pelvic inflammatory disease; vaginal, vulvar, and anal warts; and perineal/perianal herpes.

Women also should be evaluated for risk of breast cancer, for contraceptive needs, and for preconception counseling

Table 2: Routine Gynecologic Screening and Counseling for Women

Medical Service	Comments
Cervical and anal cancer screening	<p>Women with HIV infection should have more frequent screening than uninfected women:</p> <ul style="list-style-type: none"> • Screen all HIV-infected women for cervical cancer (cervical Pap test) at initial visit, at 6 months, then annually unless abnormal. • For HIV-infected women (any age) with ASCUS or higher-grade abnormality, colposcopy generally is recommended; alternatively, the Pap can be repeated in 6-12 months. • Consider anal cancer screening (anal Pap test) for all HIV-infected women if high resolution anoscopy is available to evaluate abnormal findings. <ul style="list-style-type: none"> • See chapters <i>Cervical Dysplasia</i> and <i>Anal Dysplasia</i> • Perform pelvic examination. <ul style="list-style-type: none"> • Include vulvar and anal examination • Assess for potentially dysplastic lesions • CDC recommendations for HPV vaccination of children and young women should be followed.
STD screening	Gonorrhea, chlamydia, syphilis at least annually, and more frequently depending on risk factors or symptom exam findings
Breast cancer screening	<p>Mammography</p> <ul style="list-style-type: none"> • Mammogram every 1-2 years recommended for women 50-69 years of age • Consider annual mammogram for women 40-50 years of age • Consider starting earlier if risk factors are present • For women ≥ 70 years of age, decisions about whether to continue screening should take into account the woman's life expectancy and clinical status <p>Clinical breast examination</p> <ul style="list-style-type: none"> • Annually <ul style="list-style-type: none"> • Breast self-examination (BSE) monthly (assess technique)
Contraceptive counseling	<ul style="list-style-type: none"> • Assess life dynamics and need for contraception at every visit. • Stop only after hysterectomy or sterilization. • See "Contraception," below.
Preconception counseling	<p>Annually or more often for all women of reproductive age</p> <ul style="list-style-type: none"> • Ask about pregnancy desires at every visit • See "Preconception Counseling," below

Contraception

Many contraceptive choices are available for HIV-infected women; some considerations are presented in the table below. For more information about interactions between ARVs and hormonal agents, see chapter *Antiretroviral Medications and Hormonal Contraceptive Agents*. Depending on the woman's (and her partner's) risk factors, consistent condom use should be emphasized, with or

without other methods of contraception, to prevent the transmission of HIV and the acquisition or transmission of other STDs. Dual contraception (e.g., use of condoms plus additional contraception) is the optimal contraceptive strategy for serodiscordant heterosexual couples since it reduces the risk of transmission of HIV and other STDs as well as providing effective contraception.

Table 3: Advantages and Disadvantages of Various Contraceptives

Contraceptive Type	Advantages	Disadvantages
Barrier Methods		
Male and female condom	<ul style="list-style-type: none"> • Only contraceptive method that also protects against transmission of HIV and STDs 	<ul style="list-style-type: none"> • Requires partner cooperation and correct technique • High failure rate when used incorrectly or inconsistently
Diaphragm and cervical cap		<ul style="list-style-type: none"> • Requires correct technique • High failure rate when used incorrectly or inconsistently • Use of diaphragms with spermicide can disrupt the cervical mucosa, which may increase risk of HIV transmission to uninfected sex partners
Hormonal Methods*		
Oral	<ul style="list-style-type: none"> • Very effective contraception if used as prescribed • Lighter menstrual flow 	<ul style="list-style-type: none"> • Do not prevent STD or HIV transmission • May have significant drug-drug interactions with PIs, some NNRTIs, and elvitegravir/cobicistat that may affect the efficacy and toxicity of estradiol or the progestin, and of certain PIs* • Alternative or additional methods recommended for women taking certain PIs or NNRTIs, or elvitegravir/cobicistat.
Injectable depot medroxyprogesterone acetate (DMPA, Depo-Provera)	<ul style="list-style-type: none"> • Effective contraception for 3 months • May cause amenorrhea 	<ul style="list-style-type: none"> • Concern about osteoporosis with long-term use • Irregular bleeding, especially initially • Weight gain • Limited and conflicting data show possible increased risk of HIV transmission (from HIV-infected woman to male partner) or acquisition (by uninfected woman from HIV-infected man) for women on DMPA (note: no study participants were on ART)
Transdermal (patch)	<ul style="list-style-type: none"> • Effective contraception if used as prescribed • Lighter menstrual flow 	<ul style="list-style-type: none"> • No data on pharmacokinetic interactions with ARVs, but of possible significance; use same precautions as with oral hormonal agents (see above)
Vaginal ring	<ul style="list-style-type: none"> • Effective contraception if used as prescribed 	<ul style="list-style-type: none"> • Lighter menstrual flow • No data on pharmacokinetic interactions with ARVs, but of possible significance; use same precautions as with oral hormonal agents (see above)
Intrauterine devices (IUDs) (copper IUD and levonorgestrel-containing IUD)	<ul style="list-style-type: none"> • Effective for long-term use • No evidence of increased HIV viral shedding • Progestin-releasing IUD may cause lighter menstrual flow 	<ul style="list-style-type: none"> • Possible blood loss with Copper T IUD • Insertion of IUD not recommended for women with advanced immunosuppression
Etonogestrel implant	<ul style="list-style-type: none"> • Effective • Amenorrhea 	<ul style="list-style-type: none"> • No data on pharmacokinetic interactions with ARVs, but of possible significance; Use same precautions as with oral hormonal agents (see above)

Contraceptive Type	Advantages	Disadvantages
Emergency contraception: <ul style="list-style-type: none"> Levonorgestrel Ulipristal acetate Copper T IUD 	<ul style="list-style-type: none"> Effective Appropriate for women who present 4-5 days after intercourse 	<ul style="list-style-type: none"> Efavirenz lowers levonorgestrel levels; use alternative method No data on pharmacokinetic interactions with ARVs, but of possible significance; use same precautions as with oral hormonal agents (see above) Heavy blood loss
Surgical Methods		
Bilateral tubal ligation (female)	<ul style="list-style-type: none"> Effective; permanent 	<ul style="list-style-type: none"> Does not prevent transmission of HIV or other STDs No future fertility (usually not reversible)
Vasectomy (male)	<ul style="list-style-type: none"> Effective; permanent 	<ul style="list-style-type: none"> Does not prevent transmission of HIV or other STDs No future fertility (usually not reversible)
Spermicides		
Spermicides		<ul style="list-style-type: none"> Not currently recommended Nonoxynol-9 causes mucosal damage to vagina Do not prevent transmission of HIV or other STDs

* See chapter *Antiretroviral Medications and Hormonal Contraceptive Agents* and Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. Available at aidsinfo.nih.gov/guidelines. Accessed December 1, 2013.

Preconception Counseling

As discussed above, every visit with an HIV-infected woman in her reproductive years presents an opportunity to discuss pregnancy desires and options, including gathering information about her partner. It is important to assess the couple's sexual history, sexual decision making, and control of reproductive options. The goals of preconception counseling are to improve the health of the woman prior to conception and identify, and when possible intervene around, risk factors for adverse maternal and fetal outcomes. When a woman desires pregnancy, it is important to discuss the topics listed below, with the goals of educating her and decreasing risk of HIV transmission to an HIV-uninfected partner or to the fetus. Ideally, the partner will take part in the discussion.

- Options for conception that decrease risk of HIV transmission to an HIV-uninfected partner (see below)
- Recommendations for ART before and during pregnancy, at delivery, and postpartum

- Optimization of maternal health status and suppression of HIV viral load before pregnancy
- Effect of HIV and ARVs on pregnancy and outcomes
- Effect of non-HIV-related factors (e.g., age, drug use) and other medical conditions (e.g., hypertension, diabetes, depression) on pregnancy course
- Counseling on safer sexual practices
- Counseling on other aspects of health promotion (e.g., smoking and alcohol cessation, drug treatment)
- Perinatal HIV transmission risk and prevention: ARVs for mother and infant, mode of delivery, avoidance of breast-feeding
- Treatment and care of an HIV-exposed or HIV-infected infant
- Long-term planning including advance directives and guardianship of a child if one or both parents were to become ill or die

Any history of infertility or low fertility in either the patient or her partner should be

evaluated and options for having children should be discussed, including current information on gamete donation, other assisted reproductive techniques, and adoption.

If the heterosexual couple is serodiscordant, techniques to minimize the risk of transmission to the uninfected partner should be discussed. These same techniques should be explained to couples when both partners are HIV infected, if there is a risk of transmitting different HIV “strains.” Some of the recommended techniques include the following:

- If the male partner is HIV uninfected: the woman does self-insemination of ejaculate using a syringe (no HIV exposure risk to the male partner)
- Maximal suppression of the HIV viral load of the infected partner with ART
- Screening for and treatment of STDs
- Assisted reproductive technology
 - Sperm washing with polymerase chain reaction (PCR) testing and intrauterine insemination (IUI), in vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI), if the male partner is HIV infected and the female partner is HIV uninfected

The couple should be fully educated about other options, including the following:

- Preexposure prophylaxis (PrEP) for the uninfected partner
- Estimating the time of ovulation and limiting unprotected intercourse to this period, with or without use of PrEP. This approach should be considered only if HIV viremia is maximally suppressed and intercourse is limited to times when conception is most likely.
- Postexposure prophylaxis for an uninfected partner

The CDC has issued interim guidelines on use of PrEP by heterosexually active individuals as well as a fact sheet on PrEP (see “References,”). Both address the use of PrEP during attempts to conceive. Few clinical data are available at this time to guide practice; when treating serodiscordant couples who wish to conceive using PrEP, providers should review current guidelines and consult with experts in the field.

If an HIV-infected woman who is considering pregnancy initiates ART, an appropriate regimen should be started before pregnancy, avoiding agents with increased risk of teratogenicity (e.g., efavirenz), hepatotoxicity (e.g., nevirapine, in women with CD4 counts of >250 cells/ μ L), or metabolic complications such as lactic acidosis (e.g., didanosine and stavudine). See chapter *Reducing Perinatal HIV Transmission* and the U.S. Department of Health and Human Services *Perinatal HIV Guidelines* (see “References,” below). It should be noted that most fetal organogenesis occurs in the early weeks of pregnancy, before most women know that they are pregnant. Thus, any medication with potential teratogenicity or fetal toxicity, whether an ARV or another drug, should be avoided for use by women who are intending to become pregnant or who may become pregnant. Certain medications (e.g., ribavirin) should be avoided by male partners of women who may become pregnant.

Folate supplementation to reduce the risk of neural tube defects in the developing fetus should be started at least 1 month before conception, if possible, because the neural tube forms in the early weeks of pregnancy (see chapter *Care of HIV-Infected Pregnant Women*).

Menopause

There is evidence that HIV-infected women may be more likely to undergo premature physiologic menopause. Earlier onset of menopause also is associated with non-HIV factors such as ethnicity and a history of intravenous drug use. Menopausal women are more at risk of premature bone loss, osteopenia, and osteoporosis; this risk may be increased by HIV infection and certain ARVs. If indicated, bone density screening (DEXA) should be considered.

Hormone replacement therapy (HRT), especially of long duration, has been associated with an increased risk of breast cancer and cardiovascular and thromboembolic events, and its routine use is not recommended. HRT may be considered for women who experience severe vasomotor symptoms and vaginal dryness, but should be used only for a limited period of time and at the lowest effective dosage.



Palliative Care and HIV

Background

Palliative care is not curative care, but is supportive, symptom-oriented care. It may be needed at any point in the course of disease progression to relieve patients' suffering and promote quality of life. Palliative care is important for patients with any medical condition, even if they are not actively in hospice. It may be used in conjunction with disease-specific care or as the sole approach to care. Palliative care includes the following:

- Management of symptoms (e.g., fatigue, pain)
- Treatment of adverse effects (e.g., nausea, vomiting)
- Psychosocial support (e.g., depression, advance care planning)
- End-of-life care

The U.S. Health Resources and Services Administration (HRSA) HIV/AIDS Bureau Working Group on Palliative Care in HIV has provided the following working definition of palliative care:

Palliative care is patient- and family-centered care. It optimizes quality of life by active anticipation, prevention, and treatment of suffering. It emphasizes use of an interdisciplinary team approach throughout the continuum of illness, placing critical importance on the building of respectful and trusting relationships. Palliative care addresses physical, intellectual, emotional, social, and spiritual needs. It facilitates patient autonomy, access to information, and choice.

(Excerpted from: HRSA Working Group on HIV and Palliative Care. *Palliative and Supportive Care*. HRSA Care ACTION, July 2000)

Palliative care for patients with HIV infection comprises a continuum of treatment consisting of therapy directed at AIDS-related illnesses (e.g., infection or malignancy) and treatments focused on providing comfort and symptom control throughout the lifespan. This care may involve multidimensional and multidisciplinary services, including HIV medicine, nursing, pharmacy, social work, complementary or alternative medicine, and physical therapy.

Palliative Care in the Era of Antiretroviral Therapy

With advances in HIV-specific therapy and care, HIV infection is no longer a rapidly fatal illness. Instead, patients who are able to tolerate antiretroviral therapy (ART) usually experience a manageable, chronic illness.

The death rate from AIDS, however, continues to be significant: approximately 15,000 deaths per year in the United States. In many parts of the world, patients still are not able to obtain specific treatments for HIV or for opportunistic illnesses, and supportive or palliative care may be the primary mode of care available to patients with advanced AIDS. Regardless of access to disease-specific treatment, people living with HIV continue to experience symptoms from HIV disease and its comorbid conditions, and those taking ART may experience adverse effects. Integrating palliative care and disease-specific care is important for treating patients with HIV in order to promote quality of life and relieve suffering.

S: Subjective

The patient with advanced HIV disease complains of one or more of the following:

- Agitation
- Anorexia
- Chronic pain
- Constipation
- Cough
- Decubitus ulcers or pressure sores
- Delirium
- Dementia
- Depression
- Diarrhea
- Dry mouth
- Dry skin
- Dyspnea
- Fatigue
- Fever
- Hiccups
- Increased secretions (“death rattle”)
- Nausea
- Pruritus
- Sleep disturbance
- Sweats
- Vomiting
- Weakness
- Weight loss

O: Objective

Conduct a complete symptom-directed physical examination.

To evaluate pain, please refer to chapter *Pain Syndrome and Peripheral Neuropathy*.

A/P: Assessment and Plan

Treatment

Common symptoms of persons with late-stage HIV infection and their possible causes are listed in Table 1. Also included are disease-specific treatments and palliative interventions. Depending on the situation, either or both of these types of treatments may be appropriate. Consider the patient’s disease stage and symptom burden, the risks and benefits of therapies, and the patient’s wishes.

When assessing each of the patient’s symptoms, include the psychiatric review of symptoms (depression, anxiety, psychosis), and consider the following aspects of each symptom:

- Onset, progression, frequency, severity
- Degree of distress and impact on function
- Aggravating and alleviating factors
- Previous treatments and their efficacy
- What the patient believes is causing the symptom
- Coping strategies and supports
- The patient’s personal goals of care with this particular symptom

Practitioners should note that some of the palliative treatments may have substantial long-term adverse effects and should be used to alleviate symptoms only in late-stage or dying patients.

Table 1. Common Symptoms in Patients with AIDS and Possible Disease-Specific and Palliative Interventions

Symptom	Possible Causes	Disease-Specific or Curative Treatment	Palliative Treatment
CONSTITUTIONAL			
Fatigue, weakness	<ul style="list-style-type: none"> • AIDS • Opportunistic infection • Anemia • Hypoandrogenism 	<ul style="list-style-type: none"> • ART • Treat specific infections • Erythropoietin, transfusion • Testosterone/ androgens in men with concomitant hypogonadism; for women, androgens are investigational and not approved by the U.S. Food and Drug Administration for this use 	<ul style="list-style-type: none"> • Psychostimulants: give in the morning; also useful as treatment for depression and sedation owing to opioids; avoid in patients with anxiety and agitation (e.g., methylphenidate, dextroamphetamine, modafinil; pemoline is not first-line because of hepatotoxicity risk) • Corticosteroids (prednisone, dexamethasone)
Weight loss/ anorexia	<ul style="list-style-type: none"> • HIV • Malignancy 	<ul style="list-style-type: none"> • ART • Specific treatment of malignancy • Nutritional support 	<ul style="list-style-type: none"> • Testosterone/androgens in men with hypogonadism (see above) • Oxandrolone for 2-4 week courses; an anabolic steroid that may be a useful adjunct, can help increase lean body mass but also has virilizing effects • Megestrol acetate can improve appetite and fatigue but has not been shown to improve nutritional status; possible adverse effects include deep vein thrombosis, glucose intolerance, and hypoandrogenism in men • Dronabinol is a cannabinol derivative that helps increase appetite but over the long term (≥ 12 months) does not significantly increase weight • Recombinant human growth hormone can improve lean body mass, but is associated with significant side effects (headache, edema, myalgias) and is expensive; consider for patients with severe wasting if no other therapies are effective • Corticosteroids can help increase appetite in the short term but not increase weight, and the duration of effect is short-lived

Symptom	Possible Causes	Disease-Specific or Curative Treatment	Palliative Treatment
Fevers, sweats	<ul style="list-style-type: none"> Disseminated <i>Mycobacterium avium</i> complex and other infections (opportunistic or other) Lymphoma and other malignancies Immune reconstitution inflammatory syndrome Medication reaction 	<ul style="list-style-type: none"> Specific treatment of opportunistic infection or malignancy ART Discontinue causative medication (if drug reaction) 	<ul style="list-style-type: none"> Acetaminophen NSAIDs (ibuprofen, naproxen, indomethacin) Anticholinergics can be useful for sweats (hyoscyamine, glycopyrrolate) H2 antagonists can be useful for sweats (ranitidine, famotidine; dose at least 12 hours apart from atazanavir or rilpivirine; note that cimetidine should be avoided in patients taking fosamprenavir or delavirdine because of drug interactions)
PAIN			
Nociceptive, somatic, visceral	<ul style="list-style-type: none"> Opportunistic infections HIV-related malignancies, nonspecific 	<ul style="list-style-type: none"> Specific treatment of disease entities 	<ul style="list-style-type: none"> See chapter <i>Pain Syndrome and Peripheral Neuropathy</i> for detailed treatment options Refer to the World Health Organization (WHO) analgesic ladder: NSAIDs and opioids Corticosteroids can be useful for treating inflammatory-mediated pain, often as an adjunct to opioids (may worsen some conditions) Benzodiazepines or muscle relaxants for muscle spasms (clonazepam, diazepam, baclofen) Nonpharmacologic therapies (e.g., massage, physical therapy)
Neuropathic	<ul style="list-style-type: none"> HIV-related peripheral neuropathy Cytomegalovirus Varicella-zoster virus Medications (e.g., stavudine, isoniazid, vincristine) 	<ul style="list-style-type: none"> ART Discontinue offending medication Change antiretroviral or other regimen 	<ul style="list-style-type: none"> See chapter <i>Pain Syndrome and Peripheral Neuropathy</i> for detailed treatment options Refer to the WHO analgesic ladder: NSAIDs and opioids Neuropathic pain medications: <ul style="list-style-type: none"> Tricyclics (nortriptyline, imipramine) Anticonvulsants (gabapentin, pregabalin, lamotrigine) Muscle relaxants (e.g., baclofen) Benzodiazepines can be useful adjuncts (clonazepam, diazepam) Corticosteroids can be useful for treating inflammatory-mediated pain, often as an adjunct to opioids (may worsen some conditions) Acupuncture

Symptom	Possible Causes	Disease-Specific or Curative Treatment	Palliative Treatment
GASTROINTESTINAL			
Nausea, vomiting	<ul style="list-style-type: none"> • Antiretroviral medications • Esophageal candidiasis • Cytomegalovirus esophagitis 	<ul style="list-style-type: none"> • Specific treatment of disease entities • Change antiretroviral regimen 	<ul style="list-style-type: none"> • Dopamine antagonists (prochlorperazine, haloperidol) • Prokinetic agents (metoclopramide) • Serotonin antagonists (granisetron, ondansetron, dolasetron) • Antihistamines (diphenhydramine, promethazine, meclizine) • Anticholinergics (hyoscyamine, scopolamine) • Somatostatin analogues in patients with bowel obstruction, to reduce gut motility; can be used with anticholinergics (octreotide) • Benzodiazepines (lorazepam) • Marijuana, dronabinol can help increase appetite
Diarrhea	<ul style="list-style-type: none"> • <i>Mycobacterium avium</i> complex • Cryptosporidiosis • Cytomegalovirus colitis • Microsporidiosis • Other intestinal infections • Malabsorption • Medications (e.g., protease inhibitors) 	<ul style="list-style-type: none"> • Specific treatment of disease entities • Discontinue offending medication 	<ul style="list-style-type: none"> • Bismuth, methylcellulose • Psyllium • Kaolin • Diphenoxylate + atropine • Loperamide • Calcium carbonate • Ferrous sulfate • Tincture of opium for severe chronic diarrhea unresponsive to other therapies • Crofelemer for ARV-related diarrhea • Octreotide for profuse, refractory watery diarrhea; expensive and needs subcutaneous administration
Constipation	<ul style="list-style-type: none"> • Dehydration • Malignancy • Anticholinergic medications • Opioids • Reduced activity 	<ul style="list-style-type: none"> • Hydration • Radiation and chemotherapy • Medication adjustment 	<ul style="list-style-type: none"> • Activity/diet modification • Prophylaxis for patients taking opioids with docusate + senna • Peristalsis-stimulating agents: <ul style="list-style-type: none"> • Anthracenes (senna) • Polyphenolics (bisacodyl) • Softening agents: <ul style="list-style-type: none"> • Surfactant laxatives (docusate) • Bulk-forming agents (bran, methylcellulose) • Osmotic laxatives (lactulose, sorbitol) • Saline laxatives (magnesium hydroxide)

Symptom	Possible Causes	Disease-Specific or Curative Treatment	Palliative Treatment
RESPIRATORY			
Dyspnea	<ul style="list-style-type: none"> • <i>Pneumocystis jiroveci</i> pneumonia • Bacterial pneumonia • Anemia • Pleural effusion, mass, or obstruction • Decreased respiratory muscle function 	<ul style="list-style-type: none"> • Specific treatment of disease entities • Erythropoietin, transfusion • Drainage, radiation, or surgery 	<ul style="list-style-type: none"> • Use of fan, open windows • Relaxation techniques, massage, guided imagery • Oxygen supplement titrated to comfort, if the patient is hypoxic • Bronchodilators (albuterol, ipratropium, inhaled steroids) if there is bronchospasm • Opioids, particularly morphine, to decrease sense of air hunger and respiratory rate • Benzodiazepines (e.g., lorazepam) to reduce the anxiety that often accompanies dyspnea
Cough	<ul style="list-style-type: none"> • <i>Pneumocystis jiroveci</i> pneumonia • Bacterial pneumonia • Tuberculosis • Acid reflux • Postnasal drip 	<ul style="list-style-type: none"> • Specific treatment of disease entities 	<ul style="list-style-type: none"> • Cough suppressants (dextromethorphan, codeine, hydrocodone, morphine, aerosolized lidocaine) • Bronchodilators (albuterol, ipratropium, inhaled steroids) if there is bronchospasm • H2 blockers or proton-pump inhibitors (ranitidine, omeprazole) if there is acid reflux (caution: interactions with atazanavir, rilpivirine) • Decongestants (pseudoephedrine, phenylephrine, steroid nasal sprays) for postnasal drip
Increased secretions ("death rattle")	<ul style="list-style-type: none"> • Fluid shifts • Ineffective cough • Sepsis • Pneumonia 	<ul style="list-style-type: none"> • Antibiotics as indicated 	<ul style="list-style-type: none"> • Atropine, hyoscyamine, transdermal scopolamine, glycopyrrolate • Fluid restriction, discontinue intravenous fluids
Hiccups	<ul style="list-style-type: none"> • Aerophagia (swallowing air) • <i>Candida</i> and other causes of esophagitis, including GERD • Vagus and phrenic nerve irritation • CNS mass lesions • Uremia • Alcohol intoxication • Anesthesia 	<ul style="list-style-type: none"> • Treatment of underlying etiology (e.g., antifungals for <i>Candida</i> esophagitis, acid reducers for GERD) 	<ul style="list-style-type: none"> • Metoclopramide can promote gastric emptying • Chlorpromazine (antipsychotic) can reduce the CNS response, start at low dosage to reduce the risk of dystonia and drowsiness • Baclofen can reduce the CNS response

Symptom	Possible Causes	Disease-Specific or Curative Treatment	Palliative Treatment
DERMATOLOGIC			
Dry skin	<ul style="list-style-type: none"> • Dehydration • End-stage renal disease • End-stage liver disease • Malnutrition • Medications (e.g., indinavir) 	<ul style="list-style-type: none"> • Hydration • Dialysis • Nutritional support • Discontinue offending medication 	<ul style="list-style-type: none"> • Avoid soaps, most of which dry the skin further • Emollients with or without salicylates • Emollients with urea (e.g., Ultra Mide 25) • Emollients with lactate (e.g., Lac-Hydrin) • Lubricating ointments or creams (e.g., petrolatum, Eucerin)
Pruritus	<ul style="list-style-type: none"> • Fungal infection • End-stage renal disease • End-stage liver disease • Dehydration; dry skin • Eosinophilic folliculitis • Opioid side effect 	<ul style="list-style-type: none"> • Antifungal agents (e.g., itraconazole for eosinophilic folliculitis) • Dialysis • Hydration • Topical corticosteroids 	<ul style="list-style-type: none"> • Avoid soaps and hot baths/showers • Warm compresses • Treatments for dry skin, as above • Topical agents (menthol, phenol [e.g., Sarna lotion], calamine, doxepin, capsaicin) • Antihistamines (hydroxyzine, doxepin, diphenhydramine) • Corticosteroids (topical or systemic) • Opioid antagonists (naloxone, naltrexone) can be useful for treating uremic and biliary-associated pruritus • Antidepressants • Anxiolytics • Thalidomide in intractable pruritus, but beware of side effects, including neuropathy
Decubitus ulcers, Pressure sores	<ul style="list-style-type: none"> • Poor nutrition • Decreased mobility, prolonged bed rest 	<ul style="list-style-type: none"> • Increase mobility • Enhance nutrition 	<ul style="list-style-type: none"> • Prevention (nutrition, mobility, skin integrity) • Wound protection (semipermeable film, hydrocolloid dressing) • Debridement (normal saline, enzymatic agents, alginates)

Symptom	Possible Causes	Disease-Specific or Curative Treatment	Palliative Treatment
NEUROPSYCHIATRIC			
Delirium/ agitation	<ul style="list-style-type: none"> • Electrolyte imbalances, glucose abnormalities • Dehydration • Hypoxia • Toxoplasmosis • Cryptococcal meningitis • CNS masses and metastases • Sepsis • Medication adverse effects (e.g., benzodiazepines, opioids, efavirenz, corticosteroids) • Intoxication or withdrawal 	<ul style="list-style-type: none"> • Correct imbalances • Hydration • Oxygen supplementation • Specific treatment of disease entities • Discontinue offending medications 	<ul style="list-style-type: none"> • Neuroleptics (haloperidol, risperidone, chlorpromazine) to induce sedation in severe agitation • Benzodiazepines (e.g., lorazepam, diazepam, midazolam) in the “terminal restlessness” of the last few days of life to relieve myoclonus, seizures, restlessness (Note: in some patients, these may have adverse effects)
Dementia	<ul style="list-style-type: none"> • HIV-associated dementia • Other dementia (e.g., Alzheimer dementia, Parkinson dementia, multi-infarct dementia) 	<ul style="list-style-type: none"> • ART 	<ul style="list-style-type: none"> • Psychostimulants (methylphenidate) • Memantine (NMDA antagonist) has been used in patients with Alzheimer dementia but has unclear benefit for patients with HIV-associated dementia • Low-dose neuroleptics (haloperidol, chlorpromazine) can be useful in psychotic delirium

Symptom	Possible Causes	Disease-Specific or Curative Treatment	Palliative Treatment
Depression	<ul style="list-style-type: none"> Chronic illness Reactive depression, major depression 	<ul style="list-style-type: none"> Antidepressants 	<ul style="list-style-type: none"> Antidepressants are useful when the patient has a life expectancy of several months or more: SSRIs, SNRIs, mirtazapine (useful in lowest dosages for insomnia), bupropion, (though beware of lowering the seizure threshold); note that tricyclic antidepressants are not considered first- or second-line therapy owing to side effects, though they may be useful for treating refractory melancholic or delusional depression (see chapter <i>Major Depression and Other Depressive Disorders</i> for further information, including dosages) Psychostimulants are useful for patients who have urgent, severe depression or are weeks from death (methylphenidate, pemoline, dextroamphetamine, modafinil)

Abbreviations: ART = antiretroviral therapy; CNS = central nervous system; GERD = gastroesophageal reflux disease; NMDA = N-methyl- D-aspartate; NSAID = nonsteroidal antiinflammatory drug; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Adapted from Selwyn PA, Rivard M. *Palliative care for AIDS: Challenges and opportunities in the era of highly active antiretroviral therapy*. *Innovations in End-of-Life Care*. 2002;4(3). Available at www2.edc.org/lastacts/archives/archivesmay02/ovessay.asp. Accessed December 1, 2013.

Advance Care Planning

Advance care planning involves planning for future medical care. Two main documents are produced:

- Advance directive (living will)
- Health care proxy (a person to speak for the patient or make decisions if the patient is too sick to do so)

The clinician should initiate these conversations and make referrals to helpful resources.

Patient Education

- Discuss advance care planning with patients, and the option of hospice care, if appropriate.
- Provide patients and their family members with detailed information so that they understand the illness and associated treatments.
- Instruct patients to discuss their pain or other bothersome symptoms with their health care provider.
- Encourage patients to talk with their health care provider if they are feeling anxious, depressed, or fearful.
- Discuss with patients what their death might be like. Some patients may feel relieved to be able to talk openly about their last days. Assure them that their pain will be controlled and that their health care provider will be there to help them.

Adherence

Background

For HIV-infected patients with wild-type virus who are taking antiretroviral therapy (ART), adherence to ART is the major factor in ensuring the virologic success of an initial regimen and is a significant determinant of survival. Adherence is second only to the CD4 cell count as a predictor of progression to AIDS and death. Adherence rates approaching 100% are needed for optimal viral suppression, yet the average ART adherence in the United States is approximately 70%. Individualized assessment of and support for adherence are essential for patients to be successful with ART.

Patients with suboptimal adherence are at risk not only of HIV progression, but also of the development of drug resistance (see chapter *Resistance Testing*) and consequent narrowing of options for future treatment. In one cohort study, it was estimated that drug-resistant mutations will occur in 25% of patients who report very high but not perfect (92-100%) adherence to ART. It is important to note, though, that the relationship between suboptimal adherence and resistance to antiretroviral (ARV) medications is very complex and is not thoroughly understood.

Characteristics of the ARV regimen and individual patient pharmacokinetic variables also influence the likelihood of both virologic suppression and the development of resistance mutations. For example, in patients with wild-type virus on initial ART regimens, it appears that more drug resistance occurs in regimens that are based on an unboosted protease inhibitor or a nonnucleoside reverse transcriptase inhibitor, where the genetic barrier to resistance is relatively low, than in regimens that include a ritonavir-boosted protease inhibitor. In patients with suboptimal adherence, these factors can influence outcomes of therapy more strongly.

S: Subjective

Studies indicate that health care providers' assessments of their patients' adherence often are inaccurate, so a calm and open approach to this topic is very important.

Adherence assessment is most successful when conducted in a positive, nonjudgmental atmosphere. Patients need to know that their provider understands the difficulties associated with taking an ARV regimen. Within a trusting relationship, a provider may learn what is actually happening with the patient's adherence rather than what the patient thinks the provider wants to hear. See Table 1 for examples of questions to assess adherence in patients who are on ART. For patients who are considering initiation of ART, it is important to lay the groundwork for optimal adherence in advance, and to anticipate barriers to adherence; see Table 2 for exploratory questions.

Common reasons for nonadherence include the following: experiencing adverse drug effects, finding the regimen too complex, having too many pills, having difficulty with the dosing schedule (not fitting into the daily routine), forgetting to take the medications, being too busy with other things, oversleeping and missing a dose, being away from home, not understanding the importance of adherence, and being embarrassed to take medications in front of family, friends, or coworkers. Other contributors to incomplete adherence include psychosocial issues (e.g., lack of social support, homelessness), psychiatric illness, and active substance abuse. It is important to look for these and other potential barriers to adherence. (See chapter *Initial History*.)

O: Objective

Evaluate the following:

- CD4 cell count
- HIV viral load (indicating the effectiveness of ART in suppressing viremia; an indirect indicator of adherence)
- Current drug list (including over-the-counter medications, vitamins, and herbal remedies); check for potential adverse drug-drug interactions with ARV medications
- Pharmacy refill records or missed doses remaining in pill organizers (e.g., medi-sets pill boxes, bubble packs)

A: Assessment

Assess adherence at each visit using questions such as those in Tables 1 and 2, and assessment scales such as those found in Tables 4, 5, and 6 (Appendix). Ask these questions in a simple, nonjudgmental, structured format and listen carefully to the patient to invite honesty about issues that may affect adherence. Asking about adherence over the last 3 to 7 days gives an accurate reflection of longer-term adherence.

Ideally, a multidisciplinary team that includes primary providers as well as nurses, pharmacists, medication managers, and social workers works together to evaluate and support patient adherence.

Table 1. Important Questions to Ask Patients Taking ART

- Do you manage your own medications? If not, who manages them for you?
- What HIV medications do you take and what is their dosage? When do you take these?
- What is your average daily schedule like? How well does taking your HIV medications at this time fit into your daily schedule?
- How do you remember to take your medications?
- How many doses of your HIV medication have you missed in the past 72 hours, past week, past 2 weeks, and past month?
- On a scale of 1 to 10, where would you say you are? A score of 1 indicates that you do not take your medicines as directed at all; for example, not every day or not at the same time every day; 10 indicates that you take your medications perfectly every day, at the same time every day. (Visual analog scales are also used to assess adherence; see Appendix.)
- If not a 10, what causes you not to be a 10?
- When are you most likely to miss doses?
- Do you have any adverse effects from your HIV medications? If so, what are they?
- Are you comfortable taking medications in front of others?
- What is most difficult about taking your medications?
- How do you like working with your pharmacy?

Table 2. Important Questions to Ask Patients Considering Initiation of ART

- What is your attitude toward ART?
- Do you believe that ART is effective?
- What are your biggest concerns about starting ART?
- What do you hope these medications will do for you?
- Are you ready to take the medication every day, around the same time each day?
- What is your level of commitment and motivation to take the medication every day for the rest of your life?
- Who knows about your HIV status?
- What other medications are you taking: prescription, over-the-counter, herbals?
- Are you a morning or afternoon person?
- What is your daily routine, including waking and bed times?
- How many meals and snacks do you eat per day, and at what times?
- Do you use alcohol, marijuana, cocaine, or injectable drugs? If so, how much do you use and how long have you used them?
- What are your ARV regimen preferences? What are some of the most important things you want to avoid in an ARV regimen (e.g., specific side effects, number of pills, frequency of dosing)?

The patient's self-report has been shown to be the most effective measure of adherence. Although, according to some studies, self-report of good adherence has limited value as a predictor

of good adherence; self-report of suboptimal adherence should be taken seriously and considered a strong indicator of nonadherence.

Before initiating (or changing) ART, it is important to assess the patient's readiness for ART. Patient factors that have been associated with poor adherence in the United States and western Europe include:

- Active alcohol or drug use
- Competing priorities (e.g., housing, childcare, food, work)
- Depression
- Lack of belief in treatment efficacy
- Lack of social support
- Lack of support from a partner
- Low literacy
- More advanced HIV infection
- Unstable housing
- Young age

Most of these factors are modifiable. Before starting ART, appropriate interventions should be made, and sources of adherence support should be identified to help patients overcome potential barriers to adherence.

It is important to note that sociodemographic variables such as sex, HIV risk factors, and education level generally are not associated with adherence. In addition, a history of substance or alcohol abuse is not a barrier to adherence.

Assess the patient's support system, and ask who knows about his or her HIV status. Supportive family members or friends can help remind patients to take their medications and assist with management of adverse effects. For patients who have accepted their HIV infection as an important priority in their lives, taking medications can become routine despite other potential adherence barriers such as alcohol or drug use.

Assess patients' willingness to accept and tolerate common adverse effects of ART. Patients may identify some adverse effects that they wish to avoid completely and others that they are willing to accept and manage; this may help

in tailoring the selection of ARV medications to the individual patient. Describe strategies for the management of adverse effects before starting a regimen (see chapters *Patient Education* and *Adverse Reactions to HIV Medications*), and emphasize that adverse effects often can be treated quite effectively, and that they should notify their providers if they experience them.

For patients taking ART, it is important to assess adherence at every clinic visit. Tools such as those in the Appendix to this chapter may be useful in predicting adherence. Adverse effects are a common cause of suboptimal adherence to ART. Continue to ask whether the patient has adverse effects from the ARV medications and assess his or her ability to accept and tolerate these. Work closely with the patient to treat adverse effects, and consider changes in ART if adverse effects are not tolerated. Continue to offer support to improve or maintain optimal adherence.

Before prescribing ARVs, some clinicians have their patients conduct adherence trials using placebo tablets or jelly beans to measure the patients' readiness to start therapy and their ability to adhere to a regimen. Such a trial allows patients to experience what a regimen will entail in real life, how therapy will affect their daily lifestyles, and what changes will be needed to accommodate the regimen. The shortcoming of placebo trials is that patients are not challenged with adverse effects as they might be with an actual regimen.

P: Plan

Start the ARV regimen when the patient is ready (recognizing that in some cases the need for ART is urgent). Starting it too early may result in poor acceptance of ART by the patient, inadequate adherence, failure of the regimen, and increased risk of ARV resistance. Comorbid conditions that may interfere with adherence, such as mental health issues or depression, may need to be treated initially. It is important to consider the patient's preferences and to involve her or him in selecting the drug regimen. The

regimen must fit into the patient's daily routine, and the patient must believe in the potential success of ART. It is extremely important to simplify the ARV regimen to the extent possible with once-daily regimens and the lowest number of pills (and lowest total expense to the patient), while maintaining efficacy and minimizing adverse effects; this will help to maximize adherence and avoid pill fatigue. Starting ART is rarely an emergency situation, so taking time to identify the patient's wishes for care, making a thorough readiness assessment, selecting the ARV regimen, and planning for adherence support are important measures for maximizing the likelihood of treatment success. (See Table 3 for additional suggestions.)

Table 3. Strategies for Improving Adherence to ART
<ul style="list-style-type: none"> • Use a multidisciplinary team approach • Establish a trusting relationship with the patient • Establish readiness to start ART • Assess and simplify regimens if possible • Involve the patient in ARV regimen selection • Identify potential barriers to adherence prior to starting ART • Provide mental health and substance abuse resources for the patient if needed • Provide resources to obtain prescription drug coverage • Assess adherence at every clinic visit • Use educational aids including pictures, pillboxes, and calendars • Identify the type of nonadherence and the reasons for nonadherence • Anticipate and treat adverse effects • If resources allow, select from among available effective interventions

Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. Available at aidsinfo.nih.gov/guidelines. Accessed December 1, 2103.

Patients who can identify their medications (in their own words) and describe the proper dosing and administration have higher adherence rates. Providing patient education before writing a prescription helps ensure adherence to ARV regimens. Education

can be provided in oral, written, or graphic form to assist the patient's understanding of the medications and their dosing. Basic information, including number of pills, dosages, frequency of administration, dietary restrictions, possible adverse effects, tips for managing adverse effects, and duration of therapy, will help patients to understand their ARV regimens. Patients should understand that the success of ART depends upon taking the medications every day and that very high adherence levels (in some cases perhaps >95%) are important in preventing virologic failure.

Close follow-up by telephone, clinic visits, or other contact with the patient during the first few days of therapy is useful in identifying adverse effects, assessing the patient's understanding of the regimen, and addressing any concerns before they become significant adherence barriers. Individualized interventions should be designed to optimize outcomes for each patient. Pharmacists, peer counselors, support groups, adherence counselors, behavioral intervention counselors, and community-based case managers are useful in supporting adherence for the HIV-infected patient. Multidisciplinary teams that include nurses, case managers, nutritionists, and clinical pharmacists, in which each care provider focuses on adherence at each contact with the patient, are extremely effective, and peer support groups, in which patients share with one another their strategies for improving adherence, may be beneficial.

Many physical devices can be used to support adherence. The following are simple, inexpensive, and easy to incorporate into the routine of the HIV patient:

- Medication organizers include pillboxes and medi-sets. These are available in several shapes and sizes to fit the needs of the individual patient. They can be filled weekly so that the patient can easily determine whether a dose of medication was missed.
- Reminder devices include alarm watches, beepers, and cell phone alarms. They are ef-

fective in reminding the patient when to take medications. Medication diaries may be used for the patient to record doses that were taken.

- Visual medication schedules are calendars featuring photos or images of the patient's medications to remind the patient which drugs to take and at what dosages.
- Interventions for successful adherence are an ongoing effort, not one-time events. Studies have suggested that adherence rates decline when patient-focused interventions are discontinued. Therefore, positive reinforcement at each clinic visit or contact is extremely important. Reinforce what the patient has done well and assist the patient in identifying and problem-solving areas for improvement. Whenever possible, share positive information about the patient's health, such as improvements in quality of life, CD4 cell count, and viral load, to encourage a high level of adherence.

Special Populations and Issues

Mental Illness

Patients with mental health issues may have difficulty with adherence. In this population, it is particularly important to incorporate ARV medications into structured daily routines. Medication cassettes, reminder signs, and calendars have been very effective for these patients. Nursing care providers and family members may be instrumental in filling medication boxes or ordering prescription refills.

Pediatrics

Adherence can be a challenge for young children who rely on parents and caregivers to provide their medications, but adolescents are more likely than younger children to have poor adherence. To improve adherence in this population, it is important to support the family. The Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* (available at aidsinfo.nih.gov/guidelines) address some of the adherence issues and considerations for this patient population.

Low Literacy

Health literacy is an important predictor of treatment adherence, particularly in low-income populations and some immigrant populations. Adherence interventions are necessary in this population to accommodate individuals who have difficulty reading and understanding medical instructions. Providers often fail to recognize this disability. In addition, adherence support is needed for patients who have difficulty navigating the health care system.

Resource-Limited Settings

Research has shown that the level of adherence in resource-limited countries is at least as good as in resource-rich settings and that rates of virologic suppression are equivalent or better. Lack of access to a consistent supply of ARV medications, including financial barriers that may cause interruptions in treatment, appears to be the primary obstacle to adherence in resource-limited settings.

Patient Education

- Educate patients about the importance of adherence and the need to take their ARV medications exactly as prescribed and to take every dose, every day.
- Advise patients that, if they miss an ARV dose on a rare occasion, that usually will not result in failure of the regimen. On the other hand, if they frequently miss or skip doses of their ARV medications, the regimen may become ineffective, and the HIV may develop resistance to ARVs.
- Tell patients to notify the clinic if they miss doses of the ARV medications.
- Work with patients to devise ways to improve their adherence, and reinforce good adherence behavior.
- Advise patients in advance that some people have adverse effects from the medications, and tell them to notify the clinic if they develop adverse effects. Discuss ways to reduce these effects.

Appendix

Table 4. Visual Analog Scale Used in a Research Study to Assess Adherence to HIV Medication Regimens

Script for Interviewing Patients About Adherence																							
Interviewer	<p>Now I'm going to ask some questions about your HIV medications.</p> <p>Most people with HIV have many pills or other medications to take at different times during the day. Many people find it hard to always remember to take their pills or medicines. For example:</p> <ul style="list-style-type: none"> • Some people get busy and forget to carry their pills with them. • Some people find it hard to take their pills according to all the instructions, such as "with food" or "on an empty stomach," "every 8 hours," or "with plenty of fluids." • Some people decide to skip taking pills to avoid adverse effects or to just not take pills that day. <p>We need to understand what people with HIV are really doing with their pills or medicines. Please tell us what you are actually doing. Don't worry about telling us you don't take all your pills or medicines. We need to know what is really happening, not what you think we "want to hear."</p> <p>Which antiretroviral medications have you been prescribed to take within the last 30 days?</p>																						
INTERVIEWER: LIST CODES FOR ALL ANTIRETROVIRALS THAT SUBJECT WAS PRESCRIBED TO TAKE IN LAST 30 DAYS. IDENTIFY UP TO 4 DRUGS.																							
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DRUG A:	DRUG C:																						
DRUG B:	DRUG D:																						
Interviewer	<p>Now, I am going to ask you some questions about these drugs. Please put an "X" on the line below at the point showing your best guess about how much (DRUGS A-D) you have taken in the last 3-4 weeks. We would be surprised if this were 100% for most people.</p>																						
HAND INSTRUMENT AND PEN TO RESPONDENT																							
Interviewer	<ul style="list-style-type: none"> • 0% means you have taken no (DRUG A) • 50% means you have taken half your (DRUG A) • 100% means you have taken every single dose of (DRUG A) 																						
Adherence Self-Assessment Instrument																							
Instructions for Patient:	<p>Put an "X" on the line below at the point showing your best guess about how much of each drug you have taken in the last 3 to 4 weeks.</p> <ul style="list-style-type: none"> • 0% means you have taken none of the drug • 50% means you have taken half of the drug • 100% means you have taken every single dose of the drug 																						
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Adapted from Machtinger EL, Bangsberg DR. *Adherence to HIV Antiretroviral Therapy*. In: Coffey S, Volberding PA, eds. *HIV InSite Knowledge Base* [textbook online]; San Francisco: UCSF Center for HIV Information; May 2005. Available at hivinsite.ucsf.edu/InSite?page=kb-03-02-09. Accessed December 1, 2013.

Table 5. Morisky Scale to Assess Adherence to HIV Medications: Dichotomous Response Options

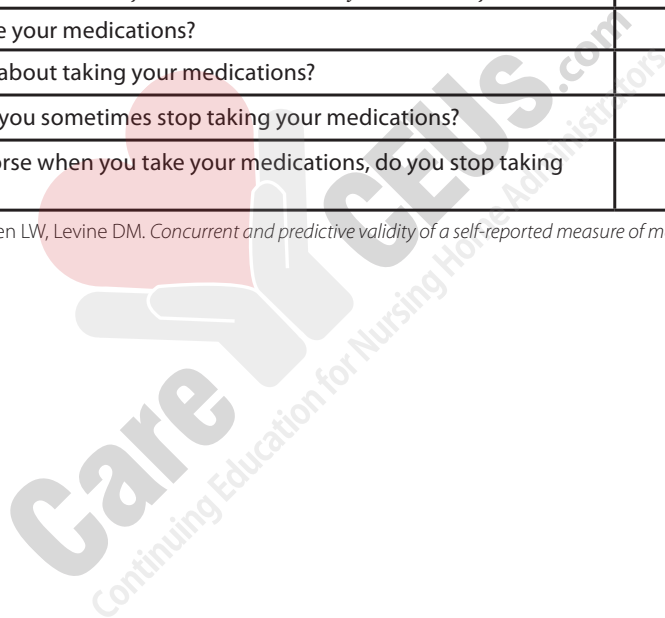
Subjects were asked: "Thinking about the medications PRESCRIBED to you by your doctor(s), please answer the following questions."	NO	YES
Do you ever forget to take your medications?		
Are you careless at times about taking your medications?		
When you feel better, do you sometimes stop taking your medications?		
Sometimes, if you feel worse when you take your medications, do you stop taking them?		

Adapted from Morisky DE, Green LW, Levine DM. *Concurrent and predictive validity of a self-reported measure of medication adherence.* Med Care 1986;24:67-74.

Table 6. Morisky Scale to Assess Adherence to HIV Medications: 5-Point Response Options

Subjects were asked: "Thinking of the medications PRESCRIBED to you by your doctor(s), please answer the following questions."	0	1	2	3	4
<i>Response options: never = 0; rarely = 1; sometimes = 2; often = 3; always = 4</i>					
Do you ever forget to take your medications?					
Are you careless at times about taking your medications?					
When you feel better, do you sometimes stop taking your medications?					
Sometimes, if you feel worse when you take your medications, do you stop taking them?					

Adapted from Morisky DE, Green LW, Levine DM. *Concurrent and predictive validity of a self-reported measure of medication adherence.* Med Care 1986;24: 67-74.





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