

HIV Update: Prevention, Treatment, Co-morbidities & Integration of Care

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Disclosures

- I have no financial relationships to disclose.
- I will not discuss off label use and/or investigational use in my presentation.

HIV/AIDS Pandemic in 2012

Over 85 million people have been infected worldwide

- Over 30 million deaths (approximately 2 million deaths per day)
- Over 33 million living with HIV infection
- 2-3 million infections annually (approximately 7,000 new infections per day)
- Number 1 cause of infectious mortality worldwide
- 4th cause of all mortality worldwide



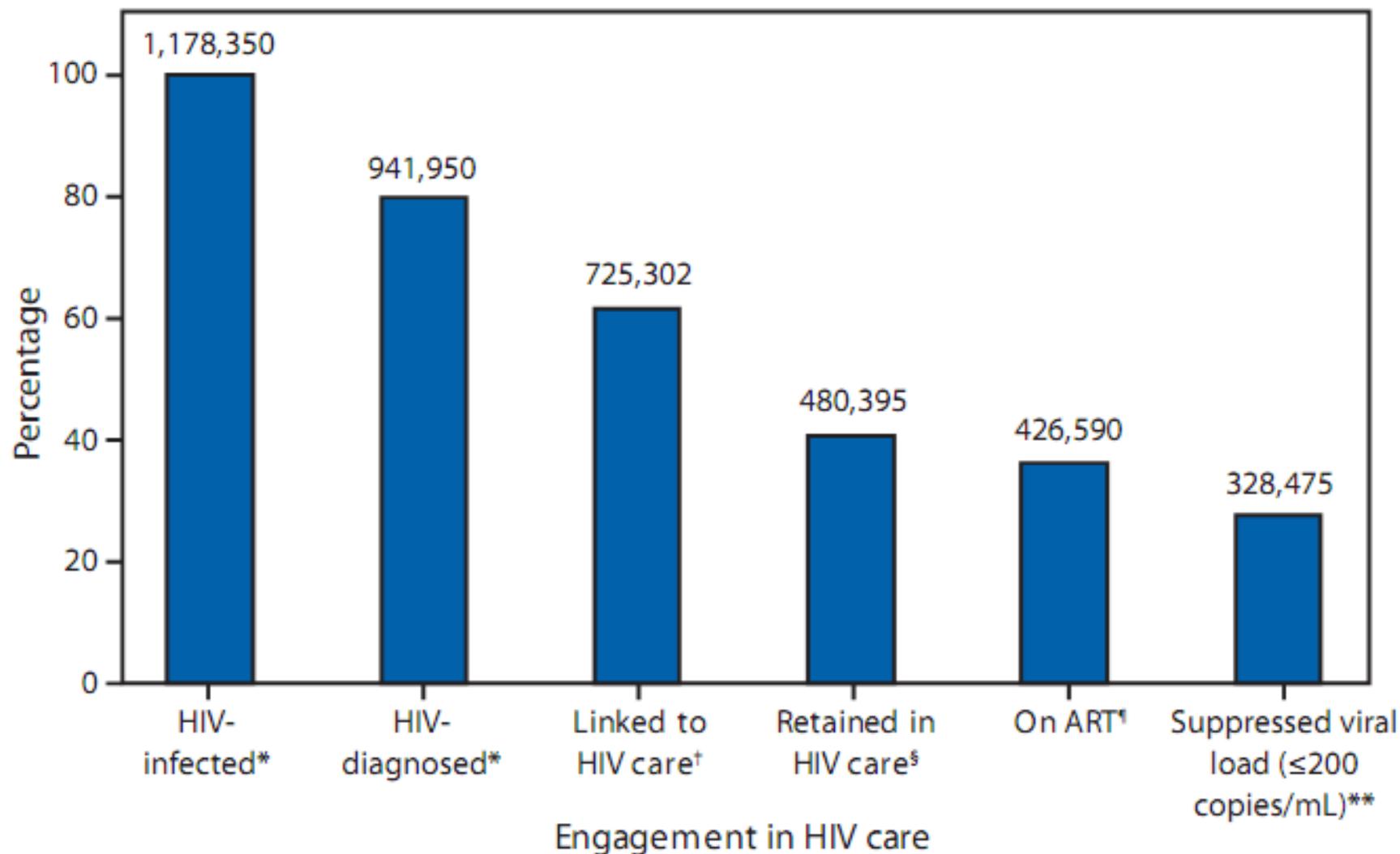
- The Centers for Disease Control and Prevention (CDC) has estimated that approximately 1.2 million adults and adolescents were living with HIV in the United States at the end of 2008
- According to the most recent incidence estimates, approximately 48,100 persons were infected with HIV in 2009
- CDC estimates that approximately 50,000 people are newly infected with HIV each year in the United States
- The estimated proportion of persons in the United States with HIV who know they are infected increased from 75% in 2003 to 80% in 2008

STATE OF ARIZONA EXECUTIVE SUMMARY

HIV/AIDS Annual Report – March 2011

- The prevalence of reported HIV infection is 216 cases per 100,000 persons in Arizona
- Currently, there are 14,265 persons living with HIV/AIDS in Arizona, a rise of 30% in 5 years

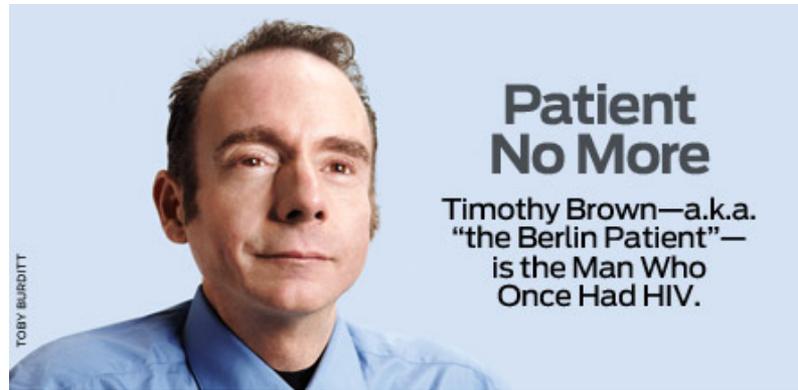
FIGURE 3. Number and percentage of HIV-infected persons engaged in selected stages of the continuum of HIV care — United States



Abbreviations: HIV = human immunodeficiency virus; ART = antiretroviral therapy.

* HIV-infected, N = 1,178,350; HIV-diagnosed, n=941,950. **Source:** CDC. HIV surveillance—United States, 1981–2008. MMWR 2011;60:689–93.

2012 Updates



Preexposure Prophylaxis for HIV — Where Do We Go from Here?



Myron S. Cohen, M.D., and Lindsey R. Baden, M.D.

- The use of antiretrovirals by HIV-uninfected persons before potential sexual exposure to HIV-infected partners is a new approach to HIV prevention termed pre-exposure prophylaxis (PrEP)
- The Food and Drug Administration (FDA) panel recently recommended approval of the TDF-FTC for PrEP based on results of the iPrEx trial (42% reduction) and the Partners PrEP trial (75% reduction) in infections when compared to placebo
- Studies of PrEP have produced both positive and negative results, but nearly all have indicated that treatment adherence is a major predictor of outcome

ORIGINAL ARTICLE

Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women

ORIGINAL ARTICLE

Preexposure Prophylaxis for HIV Infection among African Women

ORIGINAL ARTICLE

Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana

N Engl J Med 2012.

DOI: [10.1056/NEJMoa1110711](https://doi.org/10.1056/NEJMoa1110711)

Preexposure Prophylaxis for HIV — Where Do We Go from Here?

Myron S. Cohen, M.D., and Lindsey R. Baden, M.D.



- How should PrEP prophylaxis be managed?
- If PrEP is started, how and when will it be stopped?
- What messages should the health care providers provide to the patient?
- How should PrEP prophylaxis be monitored for adherence and safety?



Preexposure Prophylaxis for HIV — Where Do We Go from Here?



Myron S. Cohen, M.D., and Lindsey R. Baden, M.D.

- The potential to develop resistance to TDF-FTC may jeopardize the therapeutic use of these drugs for the patient and the community at large
- There is an increased risk of resistance if PrEP is started during acute HIV infection
- “Health care providers recommending PrEP need a plan that recognizes the effects on the patient’s sexual behavior, safety, and well-being, as well as the ramifications of the intervention for the health of the public”

FDA approves first rapid, home HIV test

July 3, 2010

The test detects the presence of HIV in saliva and provides results within 20 to 40 minutes

The home test has a sensitivity of 92.98 % and specificity 99.98 %

The test could miss one person for every 12 HIV-infected people who use the kit and requires two months post-exposure for the test to produce reliable results



New Developments



The “Quad,” is a new single-pill four-drug regimen:

- Elvitegravir/cobicistat/emtricitabine/tenofovir phase III trials have shown it as non-inferior to both TDF/FTC/EFV and TDF/FTC + ATV/r, including in high HIV RNA
- The results have been filed with the FDA the study now has been published

Dolutegravir is in ongoing Phase III studies:

- This drug has broader activity than elvitegravir and is active against both elvitegravir and raltegravir-resistant virus

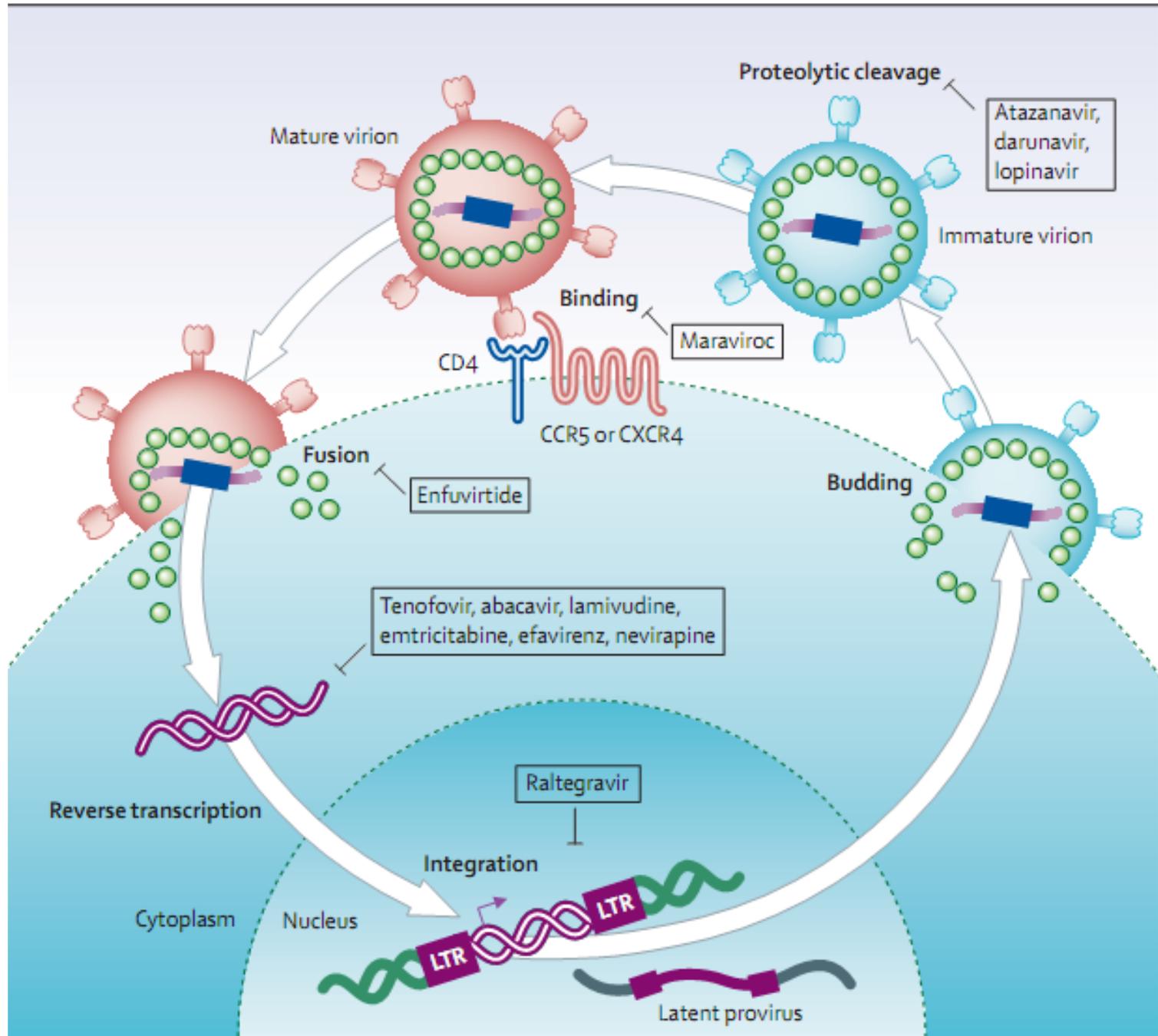


Figure 1: HIV life cycle and antiretroviral drug targets

New Developments

GS 7340 “prodrug” of tenofovir studies are ongoing:

- A 10-day monotherapy dosing study showed relative change in viral load
- The Phase 2 program is currently enrolling



“The Berlin Patient”

- His infection has been controlled without medications since 2008, after receipt of an allogeneic bone marrow transplant from a CCR5-deficient donor
- In a recent study samples of his blood and rectal biopsies were sent to various laboratories to detect any evidence of HIV but the results were mixed
- “The meaning of these results will become clear only with longer follow-up, but in the meantime, we should maintain a balanced view”

Daniel R. Kuritzkes, MD, Brigham and Women's Hospital



Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals. The strength of this recommendation varies on the basis of pretreatment CD4 cell count:
 - CD4 count <350 cells/mm³ **(AI)**
 - CD4 count 350 to 500 cells/mm³ **(AII)**
 - CD4 count >500 cells/mm³ **(BIII)**
- Regardless of CD4 count, initiation of ART is strongly recommended for individuals with the following conditions:
 - Pregnancy **(AI)** (see [perinatal guidelines](#) for more detailed discussion)
 - History of an AIDS-defining illness **(AI)**
 - HIV-associated nephropathy (HIVAN) **(AII)**
 - HIV/hepatitis B virus (HBV) coinfection **(AII)**
- Effective ART also has been shown to prevent transmission of HIV from an infected individual to a sexual partner; therefore, ART should be offered to patients who are at risk of transmitting HIV to sexual partners **(AI [heterosexuals] or AIII [other transmission risk groups]; see text for discussion).**
- Patients starting ART should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence **(AIII)**. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

March 2012

Goals of HIV Treatment

- Improve quality of life
- Reduce HIV-related morbidity and mortality
- Restore and/or preserve immunologic function
- Maximally and durably suppress HIV viral load
- Prevent HIV transmission through use of antiretroviral therapy (ART)

Recommendation to initiate therapy at CD4 count >500 cells/mm³

Growing awareness that untreated HIV may be associated with development of:

- Cardiovascular disease (CVD) and Kidney disease
- Liver disease
- Neurologic complications and Malignancy
- Availability of ART regimens that are more effective, more convenient, and better tolerated

Evidence from one observational cohort study that showed survival benefit in patients who started ART when their CD4 counts were >500 cells/mm³

Recommendations for Rapid Initiation of ART

Clinical Category or CD4 Count	Recommendation
<ul style="list-style-type: none">■ AIDS-defining illness■ Low CD4 counts <200 cells/μL■ Pregnancy■ HIV-associated nephropathy (HIVAN)■ Hepatitis B (HBV) co-infection*■ Rapidly declining CD4 counts■ Higher viral loads	Initiate ART

* Treatment with fully suppressive drugs active against both HIV and HBV is recommended.

Current ARV Medications

NRTI/NTRTI

- Abacavir (ABC)
- Didanosine (ddl)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF) NT
- Zidovudine (AZT, ZDV)

NNRTI

- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)
- Rilpivirine (RPV)

Protease Inhibitors

- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Tipranavir (TPV)

Integrase Inhibitor

- Raltegravir (RAL)

Fusion Inhibitor

- Enfuvirtide (ENF, T-20)

CCR5 Antagonist

- Maraviroc (MVC)

ART 2012

Easier, less toxic, and more potent therapy



Initial Regimens: Preferred

NNRTI based	■ EFV/TDF/FTC ^{1,2}
P. Inhibitor based	■ ATV/r + TDF/FTC ² ■ DRV/r (Daily) + TDF/FTC ²
INSTI based	■ RAL + TDF/FTC ²
Pregnant women	■ LPV/r (Twice daily) + ZDV/3TC ²

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.

2. 3TC can be used in place of FTC and vice versa. TDF should be used with caution in patients with renal insufficiency.

HIV-Infected Women

- In general, no sex differences in virologic efficacy of ART
- Some evidence of sex differences in metabolism and response to some ARVs
- Increased risk of certain ARV adverse effects:
 - NVP-associated hepatotoxicity (especially if initiated at CD4 count >250 cells/ μ L)
 - Lactic acidosis: avoid d4T + ddI
 - Metabolic complications (eg, lipoaccumulation, elevated triglycerides, osteopenia/osteoporosis)

HIV-Infected Women: Contraception

- ARV interactions with hormonal contraceptives:
 - Oral agents: PIs and NNRTIs may increase or decrease levels of ethinyl estradiol, norethindrone, and norgestimate, and may cause contraceptive failure or estrogen or progestin adverse effects
 - Few data on transdermal patch, vaginal ring: cautions as above
 - DMPA: few data; no significant interactions with ERV, NVP, NFV, NRTIs
- IUD: safe and effective

HIV and the Older Patient

- In the U.S., approximately 30% of HIV-infected persons are ≥ 50 years of age
- Aging-related comorbidities may complicate management of HIV
- HIV may increase risk of comorbidities and may accelerate the aging process
- Limited data on effects of ARVs on older persons (eg, adverse effects, drug-drug interactions)

HIV and the Older Patient:

- Reduced mucosal and immunologic defenses and changes in risk behaviors may lead to increased risk of HIV acquisition and transmission
- HIV screening rates in older persons are low
- Older persons may have more advanced HIV at presentation and ART initiation
 - Screen for HIV per CDC recommendations
 - Sexual history, risk-reduction counseling, screening for STIs (as indicated) are important to general health care for HIV-infected and HIV-uninfected older persons

HIV and the Older Patient: ART

- ART is recommended in patients >50 years of age, regardless of CD4 cell count (BIII)
- Older persons have decreased immune recovery and increased risk of non-AIDS events
- No data on specific ARVs in older persons; individualize ARV selection
- Monitor ART effectiveness and safety per general guidelines, but give special attention to renal, liver, cardiovascular, metabolic, and bone health

HIV and the Older Patient: ART

- CD4 recovery on ART may be less robust in older patients (though virologic response appears to be the same as in younger patients)
- Starting ART at younger age may result in better outcomes (immunologic and perhaps clinical)
- Interactions between ARVs and other medications, as well as polypharmacy, may complicate care

HIV and the Older Patient: Complications and Comorbidities

- Non-AIDS illnesses (eg, cardiovascular disease, liver disease, cancer, bone fragility, and neurocognitive impairment) may have increased disease burden in aging HIV-infected persons
- Current primary care recommendations advise to identify and manage risks in HIV-infected as in HIV-uninfected individuals

HBV/HIV Coinfection

- 5-10% of HIV-infected persons in the United States have chronic HBV infection
- Progression of HBV is faster with HIV coinfection (cirrhosis, ESLD, hepatocellular carcinoma [HCC])
- HBV does not alter progression of HIV infection or efficacy of ART
- In HBV/HIV coinfecting patients, liver toxicity from ARVs and flares of HBV may complicate HIV treatment

HBV/HIV Coinfection and ART

Considerations in ART:

- FTC, 3TC, and TDF are active against both HIV and HBV
 - Discontinuation may cause HBV flares
- HBV resistance to 3TC monotherapy
 - 40% at 2 years, 90% at 4 years
 - 3TC or FTC should be used in combination with other anti-HBV drugs
- Entecavir has activity against HIV; may select for M184V mutation, conferring cross-resistance to 3TC and FTC
 - Use only with fully suppressive ARV regimen

HBV/HIV Coinfection: Treatment Recommendations

For all HBV/HIV coinfecting patients:

- Counsel avoidance of alcohol
- Vaccinate against hepatitis A (if not immune)
- Advise on methods to prevent HBV transmission
- Evaluate severity of HBV infection

HCV/HIV Coinfection

- Higher rates of progressive liver disease in HIV/HCV coinfection
- Unclear whether HCV increases HIV progression
- ART may slow progression of liver disease; consider ART, regardless of CD4 count
- For most patients, benefits of ART outweigh concerns about ARV-associated hepatotoxicity

HCV/HIV Coinfection: HCV Treatment

- Boceprevir, telaprevir
 - Substrates and inhibitors of CYP 3A4/5 and p-glycoprotein; significant interactions with some ARVs
 - Some ARVs must be avoided; for others, dosage adjustment of the HCV PI may be required; consult with an expert
 - Treatment algorithms are complex; refer to a specialist

TB and HIV Coinfection: ART Recommendations

- Patients not on ART:
 - Immediately initiate TB treatment
 - If CD4 count <50 cells/ μL : start ART within 2 weeks of starting TB treatment
 - If CD4 count ≥ 50 cells/ μL and clinical disease is severe: start ART within 2-4 weeks of starting TB treatment
 - If CD4 count ≥ 50 cells/ μL and clinical disease is not severe: ART can be delayed beyond 2-4 weeks of starting TB treatment but should be started within 8-12 weeks
 - If CD4 >500 cells/ μL : above recommendations are softer (BIII)

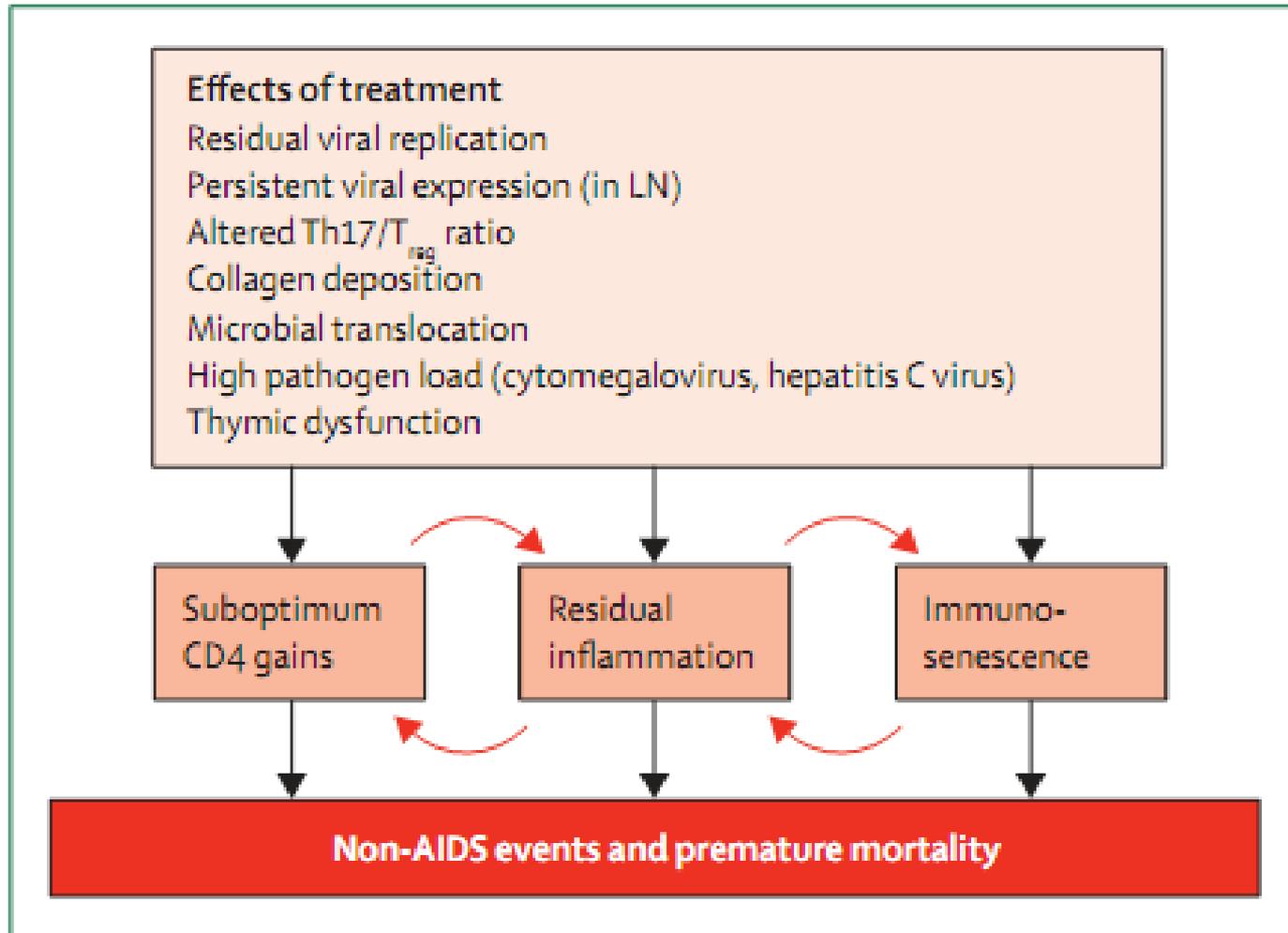
Depression and HIV Progression

- Depression (and substance use disorders) are associated with non-adherence to ART
- Controlling for adherence, depression remains associated with more rapid progression of HIV and increased morbidity and mortality
- The treatment of depression improves medical outcomes
- The diagnosis and treatment of depression is an essential component of HIV care

Increased Frequency of Non-AIDS Complications

- Cardiovascular Disease
- Metabolic Syndrome and Diabetes
- Cancer (non-AIDS)
- Bone Fracture and Osteopenia
- Liver Failure and Renal Disease
- Peripheral Neuropathy
- Cognitive Decline
- Frailty

Pathogenesis of non-AIDS morbidity and mortality during treatment



Paul A Volberding, Steven G Deeks

Lancet 2010; 376: 49-62

Dyslipidemia

- Cholesterol elevation seen in 27% pts on combination therapy (>240 mg/dl)
- Triglyceride elevation seen in 40% (>200 mg/dl)
- HDL <35 mg/dl seen in 27% of patients

Carbohydrate Metabolism

- Impaired glucose tolerance seen in more than 35% of HIV infected patients compared to 5% in age and BMI matched controls
- Diabetes Mellitus was 3.1 times as likely to develop in HIV patients treated with combination therapy versus control population

Cardiovascular Disease

- Diabetes Mellitus is considered a coronary risk equivalent
- Established risk factors
- Hypertension is seen at higher rates in patients in ART therapy than for age-matched controls
- PI therapy may promote atherosclerosis by ↑ CD-36 dependent cholesterol ester accumulation in macrophages

Prevalence of Neurologic Complications in HIV/AIDS

	%		%
• Neuropathy	25-57	• PML	<5
• Dementia	<10	• CNS Lymphoma	<5
• Mild Cognitive Impairment	>50	• Toxoplasmosis	<5
• Myelopathy	5-10	• Cryptococcal Meningitis	<5
• Myopathy	<5	• CMV CNS	<5
• Neurosyphilis	<5	• Stroke	<5
		• IRIS	???

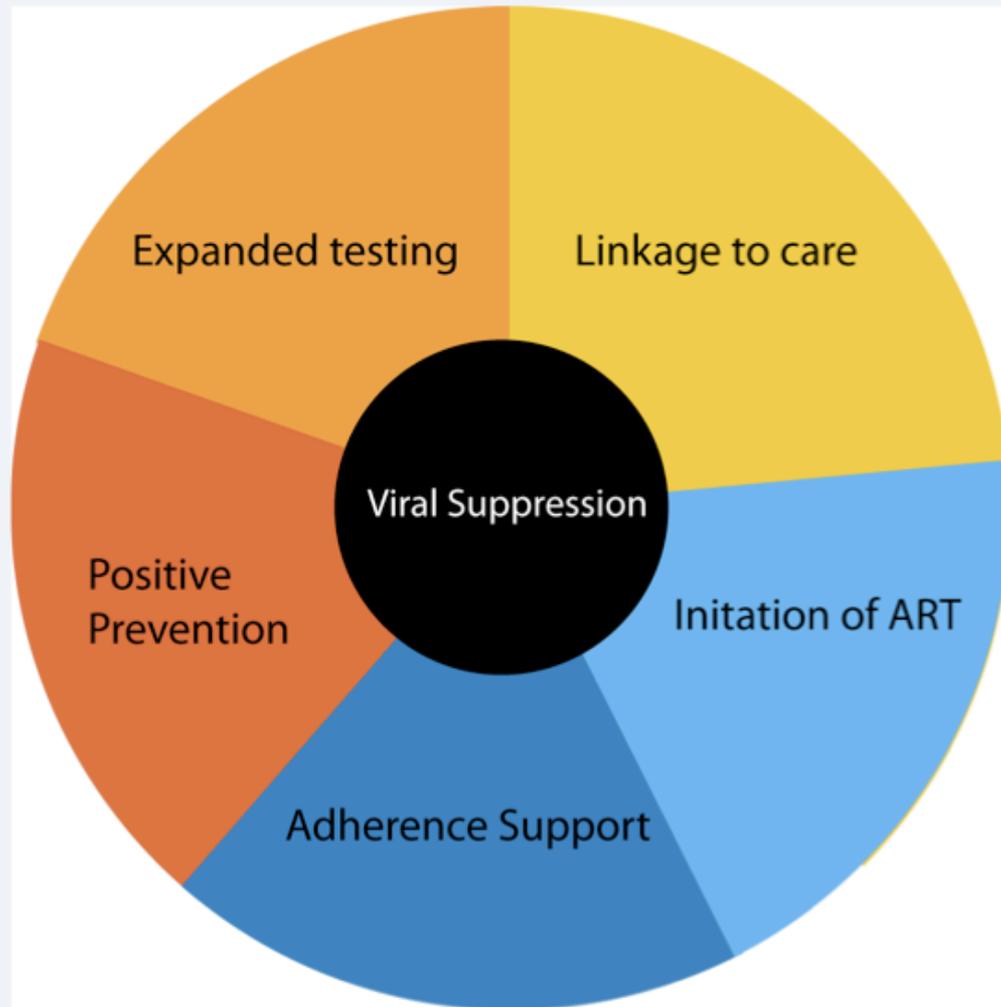
Risk Factor Modification

- Dyslipidemia
- Hypertension
- Insulin resistance
- Sedentary lifestyle
- Weight
- Family history
- Tobacco

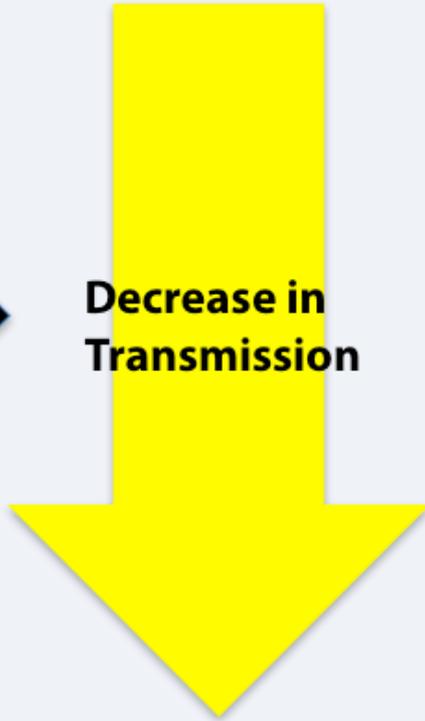
Will Complications Occur Despite Early ART?

- Cardiovascular disease: HIV is independent risk factor. Effect of untreated HIV worse than “cardiotoxic” ARV agents.
- Kidney disease: ART prevents/reverses HIVAN; CD4 predictor of kidney disease. Long-term use of TDF may cause renal impairment.
- Liver disease: ART slows progression of chronic viral hepatitis; allows optimal treatment of HBV. CD4 predictor of liver disease.
- Malignancies: Early ART likely to prevent some, but not all (e.g. Hodgkin’s).
- Neurocognitive dysfunction: ART prevents/treats dementia. Will it completely prevent cognitive dysfunction?
- Bone disease: HIV is independent risk factor for osteopenia, but decreased bone density seen with initiation of ART (greatest with TDF).

ART for Prevention is a Multi-Component Intervention



Health Systems Interventions



Revised Recommendations

Adults and Adolescents - I

- Routine, voluntary HIV screening for all persons 13-64 in health care settings (not based on risk)
- Repeat HIV screening of persons with known risk at least annually
- Opt-out HIV screening with the opportunity to ask questions and the option to decline
- Prevention counseling in conjunctions with HIV screening in health care settings is not required

Rationale for Revising Recommendations

- Many are not tested for HIV until symptomatic and effective treatments are available
- Awareness leads to substantial reductions in high-risk sexual behavior
- There is inconclusive evidence about prevention benefits of counseling for persons who test negative
- We now have a great deal of experience with HIV testing, including rapid tests

Revised Recommendations

Adults and Adolescents - II

- Intended for all health care settings, including inpatient services, EDs, urgent care, STD clinics, TB clinics, public health clinics, substance abuse treatment centers, and correctional health facilities
- Communicate test results in same manner as other diagnostic/screening tests
- Provide clinical HIV care or establish reliable referral to qualified providers

1 in 5 HIV+
Americans
DON'T KNOW IT