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General Medicine Practices for HIV/AIDS Healthcare Providers

RUSH UNIVERSITY MEDICAL CENTER

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Content Faculty

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Professor of Clinical Medicine
Division of Infectious Diseases
University of Miami School of Medicine
Miami, Florida

Learning Objectives (CME/CNE/CPE)

- Upon completion of this educational activity, participants should be able to:
  - Describe the screening and testing processes for HIV infection based on the recommendations from the Centers for Disease Control and Prevention
  - Counsel HIV-infected patients on the benefits and risks associated with antiretroviral therapy
  - Evaluate HIV-infected patients for lifestyle and other comorbidities that might impact the management of HIV disease
  - Recommend antiretroviral therapy for HIV-infected patients according to the guideline recommendations by the Department of Health and Human Services

General Medicine in HIV: Key Screening and Management Strategies

- Changing epidemiology of HIV infection
- Baseline evaluation of the HIV-infected patient and discussion of antiretroviral treatment guidelines
- Special considerations for common comorbidities in HIV
  - Metabolic issues
  - Cancer
  - Sexually transmitted disease
  - Hepatitis coinfection

Changing Epidemiology of HIV Infection

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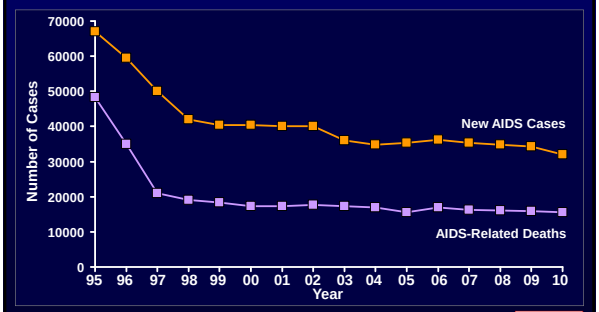
New AIDS Cases and AIDS-Related Deaths in the United States



CDC. *HIV Surveillance Report, 2011*. Available at: http://www.cdc.gov/hiv/library/reports/surveillance/2011/surveillance_Report_vol_23.html.

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CDC: Estimated HIV Prevalence in the United States (2006)

- Data from 40 States with integrated HIV and AIDS surveillance reporting
- Estimated HIV prevalence (2006)
  - 1,106,400 (95% CI 1,056,400-1,156,400)
    - 21% are undiagnosed
  - Blacks make up 46% of persons with HIV but only 12% of the general population

	Distribution of HIV Prevalence in 2006 (%)
Males	74.8
Race	
Blacks	46.1
Whites	35.0
Hispanics	17.5
Transmission category	
MSM	48.1
HRHC (female)	18.2
IDU (male)	11.9
IDU (female)	6.6
MSM-IDU	5.0
Age (y)	
13 to 24	4.4
25 to 44	51.2
45 to 54	30.5
>55	13.9

HRHC: high-risk heterosexual contact.

Campsmith ML, et al. *JAIDS*. 2010;53:619-624.

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Transformation of ART

Once-Daily, Single-Tablet Regimens

No ART

1980s
- ZDV Mono-Therapy

1990s
- Sequential NRTI Monotherapy
- Dual NRTI Therapy
- Early HAART

2000s
- Early HAART
- Treatment Interruption Trials
- Fixed-Dose Combinations
- More Potent, Durable ART
- Earlier Initiation of Therapy
- New Classes of Therapy
- Single-Tablet Regimens

2010s
- Single-Tablet Regimens
- PrEP

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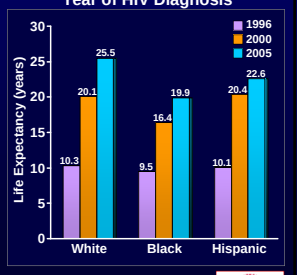
CDC Estimates (1996-2005): Life Expectancy After HIV Diagnosis

- Life expectancy for HIV patients increased from 10.5 to 22.5 years
  - Women: 23.9 years
  - Men: 22.0 years
- Average life expectancy decreased with each increasing year of age at HIV diagnosis

Life Expectancy by Year of HIV Diagnosis



Harrison KM, et al. *JAIDS*. 2010;53:124-130.

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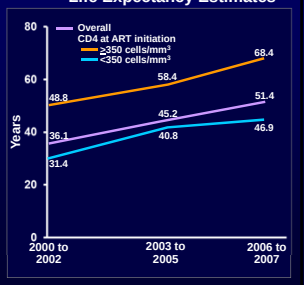
Life Expectancy Among Treated HIV Patients in the US and Canada (2000-2007)

- NA-ACCORD participants ≥20 years of age (n=22,937)
  - Treatment-naïve before initiating ART
- Crude mortality rate (2000-2007)
  - 19.8 per 1000 person-years (n=1622 deaths)
- Life expectancy at 20 years of age
  - Increased from 36.1 to 51.4 years from 2000-2002 to 2006-2007
- A 20-year-old HIV-positive person is expected to live into their early 70s

Life Expectancy Estimates



NA-ACCORD: North American AIDS Cohort Collaboration on Research and Design.

Samji H, et al. *PLoS One*. 2013 ;8:e81355.

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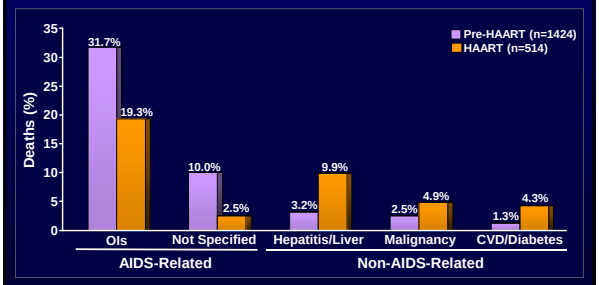
CASCADE Collaboration: Causes of Death



n=7680 seroconverters, of whom 1938 died (26%; 1424 pre-HAART and 514 during HAART).
No change in death due to AIDS-related malignancy, other infections, organ failure, and unknown causes.

Smit C, et al. *AIDS*. 2006;20:741-749.

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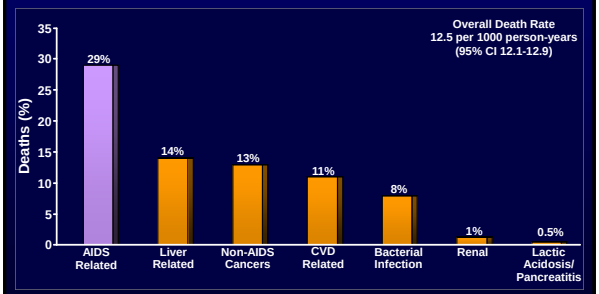
D:A:D Study: Causes of Death



n=49,734 HIV-infected patients (1999-2011).
A total of 3802 deaths over 304,695 person-years of follow-up.

Weber R, et al. 19th IAC. Washington, DC, 2012. Abstract ThAB0304.

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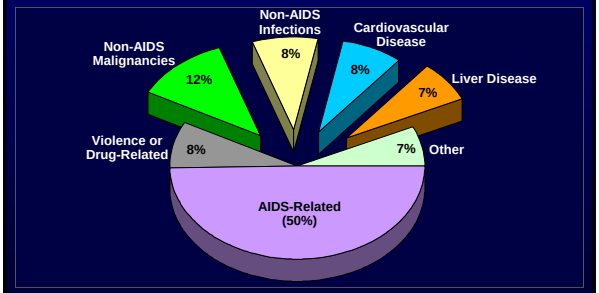
ART Cohort Collaboration: 50% of Deaths Due to Non-AIDS-Related Causes (1996-2006)



n=39,272 HIV-infected patients from 13 cohort studies in Europe and North American who were treated with antiretroviral therapy.
*Causes of death were retrospectively assigned to 85% of total deaths (1597/1876).

ART Collaboration. *Clin Infect Dis*. 2010;50:1387-1396.

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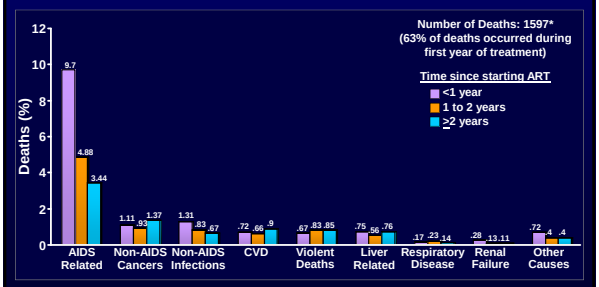
ART Cohort Collaboration: Causes of Death in ART-Treated Patients (1996-2006)



n=39,272 HIV-infected patients from 13 cohort studies in Europe and North American who were treated with antiretroviral therapy.
*Causes of death were retrospectively assigned to 85% of total deaths (1597/1876).

ART Collaboration. *Clin Infect Dis*. 2010;50:1387-1396.

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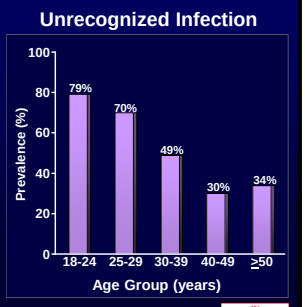
National HIV Behavioral Surveillance: Unrecognized HIV Infection

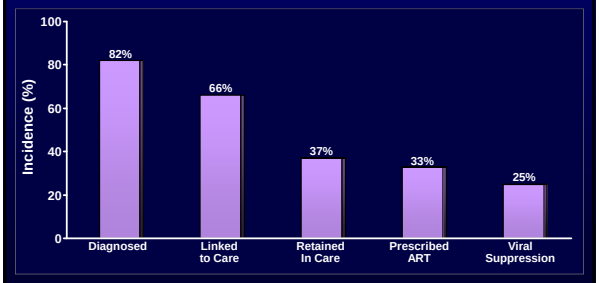
- Cross-sectional study
  - 5-city data collection system
  - Men who have sex with men
  - 83% participation rate
- Participants tested for HIV infection
  - Surveyed about knowledge of their HIV status



Branson BM, et al. *MMWR Recomm Rep*. 2006;55(RR-14):1-17.

17

CDC: HIV-Infected Persons Engaged in Selected Stages of the Continuum of Care (2009)



n=1,148,200 HIV-infected persons, 18% of whom are unaware of their infection.
Hall HI, et al. *JAMA Intern Med*, 2013;173:1337-1344.

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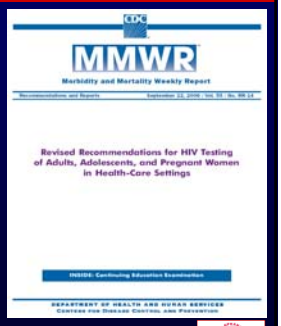
Revised CDC Recommendations for HIV Testing in Healthcare Settings

- Routine voluntary testing for patients ages 13 to 64 years in healthcare settings
  - Not based on patient risk
- Opt-out testing
- No separate consent for HIV
- Pretest counseling not required
- Repeat HIV testing left to discretion of provider
  - Based on patient risk


MMWR
Morbidity and Mortality Weekly Report

Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention

Branson BM, et al. *MMWR Recomm Rep*. 2006;55(RR-14):1-17.

19

HIV Screening: Guidelines From Other Organizations

- US Preventive Services Task Force (2013)
  - Strongly recommends clinicians screen for HIV in all adolescents and adults 15 to 65 years of age (endorsed by AAFP, but beginning at 18 years of age)
    - Younger adolescents and older adults at increased risk should also be screened
  - Recommends clinicians screen all pregnant women for HIV
- American College of Physicians (2008) (endorsed by the HIV Medicine Association)
  - Recommends clinicians adopt routine screening for HIV and encourage patients to be tested
    - Regardless of whether HIV risk factors are present
  - Recommends clinicians determine the need for repeated screening on an individual basis

US Preventive Services Task Force. AHRQ publication number 12-05173-EF-3. April 2013.
Moyer VA, et al. *Ann Intern Med*. 2013;159:51-60.
AAFP. Available at: http://www.aafp.org/patient-care/clinical-recommendations/all/hiv.html.
Qaseem A, et al. *Ann Intern Med*. 2009;150:1-8.

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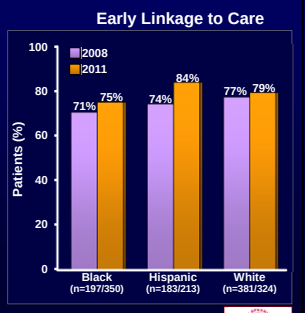
CDC: Early Linkage to Care Among MSM (2008-2011)

- US National HIV Surveillance System (20 cities)
  - MSM (n=810)
- Change in early linkage to care from 2008 to 2011
  - Prevalence did not change overall (75% to 78%)
  - Largest increase among Hispanics (74% to 84%)
  - Higher among those with higher education and income, gay versus bi/heterosexual, older age at diagnosis



Early linkage to care: clinic visit for HIV care within 3 months of diagnosis.

Hoots BE, et al. 21st CROI. Boston, 2014. Abstract 986.

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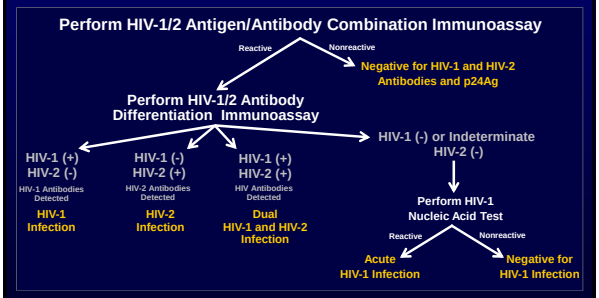
CDC and APHL: Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens



Note: new algorithm may not be uniformly adopted in all settings. If a rapid 3rd generation test is used with a positivie test result, confirmation is needed with a more specific test (eg, Western Blot).

CDC and APHL. http://stacks.cdc.gov/view/cdc/23447. Version June 27, 2014.

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Baseline Evaluation of the HIV-Infected Patient

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Baseline Evaluation

- General history
- HIV disease characteristics
- Mental health history
- Substance abuse history
- Sexual history
- Psychosocial assessment
- Review of systems

Aberg JA, et al. *Clin Infect Dis.* 2014;58:e1-e34.

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What's New With the DHHS Guidelines? Change in Frequency of CD4 Monitoring

- Essential when entering care
- Generally not required for patient management
- On ART ≥2 years with consistent viral suppression
  - 300-500 cells/mm^3: monitor every 12 months
  - >500 cells/mm^3: monitoring optional
- Resume more frequent CD4 monitoring
  - Virologic rebound, new HIV-associated clinical symptoms, develop conditions or initiate therapy that may lead to reduction in CD4 count
- Monitoring lymphocyte subsets (eg, CD8, CD19, etc) is not routinely recommended

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

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Newly Diagnosed Patient: Recommended Laboratory Tests for Initial Visit

	At Entry Into Care	Follow-Up Before HAART
HIV RNA	√	Every 3 to 6 months
Drug resistance testing Recommended for all persons with an HIV RNA >1000 copies/mL, regardless of treatment initiation Consider if HIV RNA 500 to 1000 copies/mL Genotypic assay is preferred Genotypic test for all pregnant women	√	

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

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Newly Diagnosed Patient: Recommended Laboratory Tests for Initial Visit

	Entry Into Care	Follow-Up Before HAART
Basic chemistry Serum NA, K, HCO_3, Cl, BUN, creatinine, glucose (preferable fasting)*	√	Every 6 to 12 months
Liver function (ALT, AST) Bilirubin (total and direct)	√	Every 6 to 12 months
CBC with differential	√	Every 3 to 6 months
Fasting lipid profile	√	If normal, annually
Fasting glucose	√	If normal, annually
Urinalysis	√	

*Renal function determination: include estimation of creatinine clearance using Cockcroft & Gault equation of glomerular filtration rate based on MDRD equation.

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

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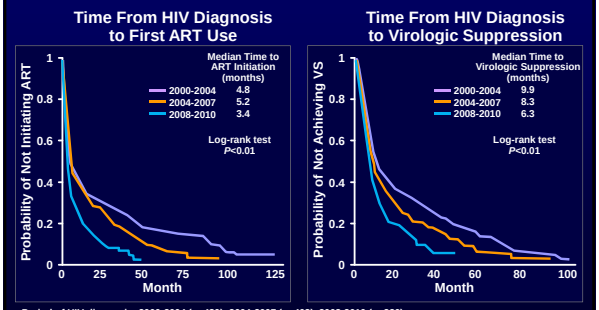
HIV Outpatient Study: Time to First ART Use and Virologic Suppression (2000-2010)



Period of HIV diagnosis: 2000-2004 (n=480); 2004-2007 (n=403), 2008-2010 (n=230).
VS: virologic suppression.

Novak RM, et al. 20th CROI. Atlanta, 2013. Abstract 1032a.

28

When to Start ART: Global Consensus and Diversity

	AIDS or HIV-Related Symptoms	CD4 Count (cells/mm³) <200	200-350	350-500	>500
United States DHHS (2014)	Yes	Yes	Yes	Yes	Yes
IAS-USA (2014)	Yes	Yes	Yes	Yes	Yes
British HIV Association (2013)	Yes	Yes	Yes	Consider	Defer
European AIDS Society (2014)	Yes	Yes	Yes	Consider	Consider
WHO (2013)	Yes	Yes	Yes	Yes	Defer

DHHS. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.
Günthard HF, et al. JAMA. 2014;312:410-425.
EACS. http://www.europeanaidsclinicalsociety.org. Revision June 2014.
BHIVA. www.bhiva.org. Revision November 2013.
WHO. http://www.who.int/publications/guidelines/hiv_aids/en/index.html. Revision June 2013.

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ART is Recommended for All HIV-Infected Individuals (DHHS)

- To reduce the risk of disease progression
  - CD4 <350 cells/mm³
  - CD4 350-500 cells/mm³
  - CD4 >500 cells/mm³
- To prevent transmission of HIV
  - Perinatal transmission
  - Heterosexual transmission
  - Other transmission risk groups

Patients starting ART should be willing and able to commit to treatment and 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

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

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ART Initiation for Patients With CD4 >500 Cells/mm^3

- Risks of HIV-associated disease progression in ART-naive patients with CD4 cell counts >500 cells/mm^3
  - Analysis is difficult because only a small proportion of individuals present for clinical care with CD4 cell counts at this level
- Studies have demonstrated a gradient of increased risk of AIDS and death when ART is initiated at lower CD4 cell count levels and have provided no evidence of a safe CD4 count level
  - Untreated HIV infection will eventually lead to immunological deterioration and increased risk of clinical disease and death

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

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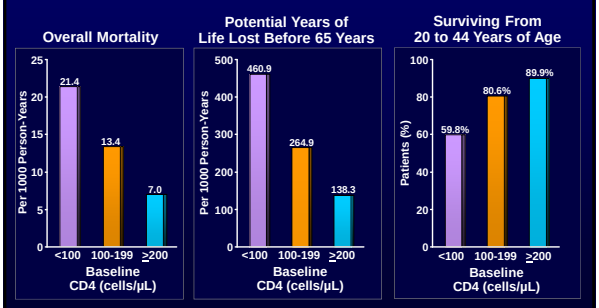
ART Cohort Collaboration: Health Indicators by Baseline CD4 Count



n=43,355 patients who initiated antiretroviral therapy between 1996 to 2005.

Antiretroviral Therapy Cohort Collaboration. *Lancet*. 2008;372:293-299.

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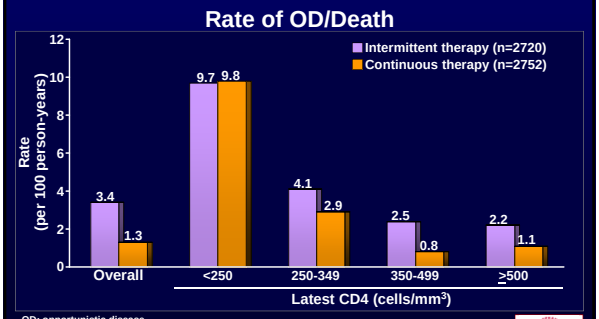
SMART Study: Continuous Treatment Reduces Rate of OD/Death



OD: opportunistic disease.

SMART Study Group. *J Infect Dis*. 2008;197:1145-1155.

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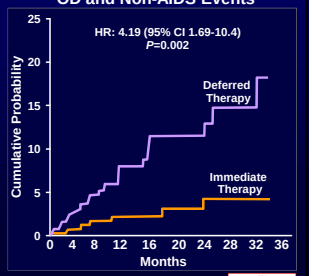
SMART Subset Analysis: Treatment-Naïve and Those not on Therapy at Baseline

- Post hoc analysis of treatment-naïve patients/not on therapy at baseline and CD4 >350 cells/mm^3
  - Defer therapy until CD4 <250 cells/mm^3 (n=249)
    - 52% treatment-naïve
  - Immediate therapy (n=228)
    - 53% treatment-naïve
- Deferring therapy associated with greater risk (hazard ratio)
  - OD: 3.26 (*P*=0.04)
  - OD/death: 3.47 (*P*=0.02)
  - Serious non-AIDS events and non-OD death: 7.02 (*P*=0.01)

Composite of OD and Non-AIDS Events



OD: opportunistic disease.

SMART Study Group. *J Infect Dis.* 2008;197:1133-1144.

34

NA-ACCORD: The Case for Earlier Initiation

- North American AIDS Cohort Collaboration on Research and Design
  - 22 HIV research cohorts from United States and Canada
- Determine all-cause mortality in patients with CD4 at 351 to 500 cells/mm^3
- Treatment arms
  - Initiate treatment with CD4 at 351 to 500 cells/mm^3
  - Deferred treatment with CD4 at 351 to 500 cells/mm^3

Baseline Characteristics

	Initiate HAART (n=2084)	Defer HAART (n=6278)
Male (%)	84	75
Age (years)	40	38
HIV RNA (log_{10} copies/mL)	4.2	4.1
Median CD4 (cells/mm^3)	422	431
HCV coinfection (%)	27	33
History of IDU (%)	15	20

Kitahata MM, et al. *N Engl J Med.* 2009;360:1815-1826.

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NA-ACCORD: Relative Hazard of All-Cause Mortality

	Relative Hazard (95% CI)	*P* Value
Deferral of HAART with CD4 at 351 to 500 cells/mm^3	1.69 (1.26-2.26)	<0.001
Female sex	1.21 (0.89-1.64)	0.24
Older age (per 10 years)	1.68 (1.48-1.91)	<0.001
Baseline CD4 cell count per 100 cells/mm^3	1.13 (0.72-1.78)	0.59

Rate of virologic suppression was similar between groups.
HIV RNA was not an independent predictor of mortality.

Kitahata MM, et al. *N Engl J Med.* 2009;360:1815-1826.

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NA-ACCORD: Survival Benefit When Initiating HAART With CD4 >500 Cells/mm^3

- Determine impact of initiating HAART at CD4 >500 cells/mm^3 on predicted survival
- Treatment arms
  - Initiate treatment with CD4 >500 cells/mm^3
  - Deferred treatment when CD4 decreases to ≤500 cells/mm^3

Baseline Characteristics

	Initiate HAART (n=2220)	Defer HAART (n=6935)
Male (%)	82	73
Age (years)	40	38
HIV RNA (log_{10} copies/mL)	3.5	3.7
Median CD4 (cells/mm^3)	679	664
HCV coinfection (%)	25	35
History of IDU (%)	14	21
HAART regimen (%)		
Unboosted PI	50	43
Boosted PI	7	9
NNRTI	32	38
Other	10	11

Kitahata MM, et al. *N Engl J Med*. 2009;360:1815-1826.

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NA-ACCORD: Improved Survival Associated With Initiating HAART With CD4 >500 Cells/mm^3

	Relative Hazard (95% CI)	*P* Value
Deferral of HAART with CD4 >500 cells/mm^3	1.94 (1.37-2.79)	<0.001
Female sex	1.85 (1.33-2.59)	<0.001
Older age (per 10 years)	1.83 (1.62-2.06)	<0.001
Baseline CD4 cell count per 100 cells/mm^3	0.93 (0.87-0.99)	0.03

As expected, both IDU and HCV coinfection were independent predictors of mortality.
HIV RNA was not an independent predictor of mortality.

Kitahata MM, et al. *N Engl J Med*. 2009;360:1815-1826.

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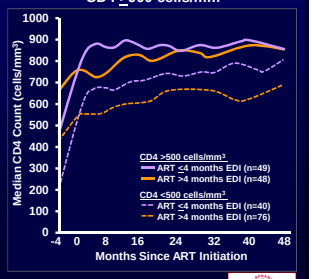
San Diego Primary Infection Cohort: Enhanced CD4 Recovery With Earlier ART

- Prospective, observational study
  - Acute or early HIV infection
  - No ART, median CD4 (cells/mm^3)
    - At EDI: 495
    - 4 months after EDI: 763
    - 12 months after EDI: <495
- Recovery to CD4 ≥900 cells/mm^3
  - Achieved more frequently when ART was initiated ≤4 versus >4 months EDI
    - 64% versus 34% (*P*<0.001)
  - Occurred faster when ART was initiated ≤4 months of EDI
    - Greatest benefit with CD4 >500 cells/mm^3 at time of initiating ART
  - No association between HIV RNA level at time of ART initiation and CD4 recovery

ART Timing and Achieving CD4 ≥900 cells/mm^3



EDI: estimated date of infection.
Le T, et al. *N Engl J Med*. 2013;368:218-230.

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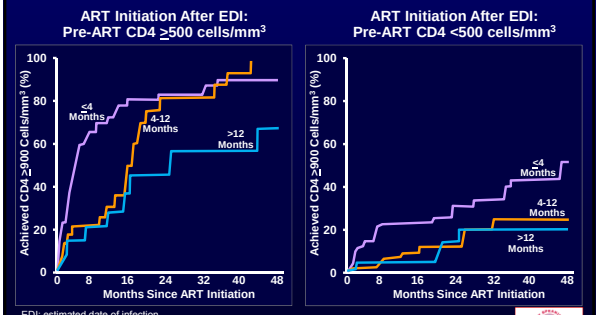
San Diego Primary Infection Cohort: Restoring CD4 ≥900 Cells/mm³



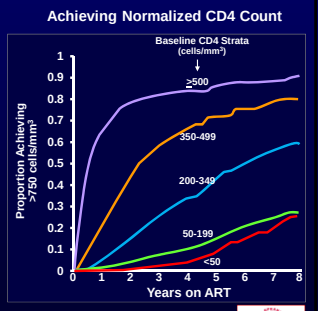
EDI: estimated date of infection.

Le T, et al. *N Engl J Med*. 2013;368:218-230.

40

HOPS Cohort: ART Initiation and Achieving CD4 Normalization

- CD4 trajectories in the HOPS Cohort after ≥3 years of ART (n=1327) (1996-2012)
  - CD4 normalization (>750 cells/mm³)
- After 7.9 years of follow-up, progressively higher CD4 at ART initiation was associated with
  - Greater gains in CD4
  - Greater likelihood of CD4 normalization (baseline CD4 and hazard ratio for achieving CD4 normalization with ART)
    - ≥500 cells/mm³: 12.8 (*P*<0.001)
    - 350-499 cells/mm³: 6.0 (*P*<0.001)
    - 200-349 cells/mm³: 2.83 (*P*<0.001)
    - Reference: 50-199 cells/mm³: 1.0
  - Increased survival rates



Palella FJ, et al. 21st CROI. Boston, 2014. Abstract 560.

41

Meta-Analysis: Efficacy of Initial ART for HIV Infection

- Prospective trials, ≥48 weeks duration
  - Treatment-naïve patients (n=40,124)
  - ITT efficacy analysis
  - Databases (to 12/2012): MEDLINE, clinical trial registries, conference abstracts, product labels, study synopses from manufacturers
- Endpoints
  - Primary
    - HIV RNA <50 copies/mL
  - Secondary
    - Efficacy by duration (48, 96, 144 weeks); DHHS guidelines (preferred versus alternative); baseline HIV RNA (≥100K versus <100K copies/mL)
    - Predictors of efficacy and failure

Baseline ART	Overall (%)
NRTI backbones (%)	
ZDV/3TC	27.0
FTC/TDF	25.2
d4T/3TC	9.9
ABC/3TC	13.7
d4T/ddI	5.9
TDF/3TC	4.9
Third drug classes (%)	
NNRTI	48.6
PI (boosted)	24.2
PI (unboosted)	14.2
NRTI	4.4
Integrase inhibitor	5.4

Lee FJ, et al. 7th IAS Conference. Kuala Lumpur, 2013. Abstract WeAB0104.

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Meta-Analysis: Outcomes With Initial ART for HIV Infection

	Overall (n=40,124)	DHHS Guidelines* Preferred (n=5677)	Alternative (n=8556)	Other (n=25,891)
Mean follow-up (weeks)	82	99	86	77
ART efficacy (%)	60	75	65	55
ART cessation (%)				
Overall	25	20	25	27
Adverse events	8.1	5.3	7.3	9.0
Patient decision	11.0	9.0	11.0	11.0
Virologic failure	3.5	3.6	2.8	3.7
Other	4.7	3.4	4.5	5.0

*Mean efficacy difference preferred versus alternative: 10% (7.6-15.4; *P*<0.001).
Similar efficacy across DHHS preferred regimens, although a trend towards superior efficacy with raltegravir.

Lee FJ, et al. 7th IAS Conference. Kuala Lumpur, 2013. Abstract WeAB0104.

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Meta-Analysis: Summary

- Overall mean efficacy was 60% over 82 weeks
  - Improved significantly over time (from 1994 to 2010), suggesting improvements in efficacy as regimens became more potent, better tolerated, and more convenient
    - Higher efficacy rates with DHHS preferred regimens (75% over 99 weeks)
- Treatment determinants of greater efficacy success
  - FTC/TDF (versus ABC/3TC);
  - NNRTIs (versus NRTI and unboosted PI)
  - Integrase inhibitor (versus NNRTI or boosted PI)
- Suboptimal efficacy
  - Most patients will interrupt ART initially
  - Pre-treatment HIV RNA ≥100K copies/mL
- Limitations
  - Unit of analysis was treatment group, not individual patients
  - Only some unpublished study data were available
  - Efficacy by HIV RNA not randomized and no analysis of individual drugs within the third drug class, clinical outcomes, or resistance
  - Lack of multivariate analysis

Lee FJ, et al. 7th IAS Conference. Kuala Lumpur, 2013. Abstract WeAB0104.

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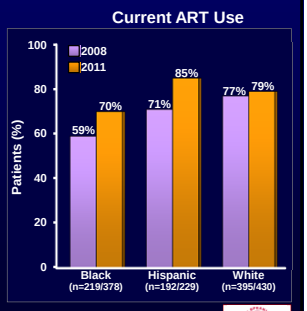
CDC: Current ART Use Among MSM (2008-2011)

- US National HIV Surveillance System (20 cities)
  - MSM (n=810)
- Change in ART use from 2008 to 2011
  - Prevalence increased overall (68% to 77%)
  - Largest increase among blacks
  - Higher increases among whites, older age groups, MSM with insurance, gay versus bi/heterosexual
  - Whites were 1.2 times more likely to be on ART than blacks



Current ART use: reported during a National HIV Behavioral Surveillance System interview.

Hoots BE, et al. 21st CROI. Boston, 2014. Abstract 986.

45

DHHS Guidelines: Regimen Classification for Treatment-Naïve Patients

- Recommended regimens
  - Regardless of baseline HIV RNA or CD4
  - Additional options for baseline HIV RNA <100K copies/mL
- Alternative regimens
- ART no longer recommended for initial therapy
  - NRTI: zidovudine
  - NNRTI: nevirapine
  - PI: unboosted atazanavir, fosamprenavir or saquinavir + ritonavir
  - Entry inhibitor: maraviroc

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

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DHHS Guidelines: Recommended Regimens

Regardless of Baseline HIV RNA Level or CD4 Count

NNRTI	Efavirenz/emtricitabine/tenofovir DF*
PI	Atazanavir + ritonavir + emtricitabine/tenofovir DF Darunavir + ritonavir (qd) + emtricitabine/tenofovir DF
INSTI	Raltegravir + emtricitabine/tenofovir DF Elvitegravir/cobicistat/emtricitabine/tenofovir DF* Dolutegravir + abacavir/lamivudine Dolutegravir + emtricitabine/tenofovir DF

*Available as a once-daily, single-tablet regimen.
Notes:
Efavirenz: avoid use in women trying to conceive or are sexually active and not using contraception.
Lamivudine may substitute for emtricitabine or visa versa.
Tenofovir DF: use with caution in patients with renal insufficiency.
Atazanavir + RTV: absorption depends on food and low gastric pH.
Elvitegravir/cobicistat/emtricitabine/tenofovir DF: only for patients with pre-ART creatinine clearance $\geq$70 mL/min.
Abacavir: only for patients who are HLA-B*5701 negative.

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

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DHHS Guidelines: Recommended Regimens

Additional Options When Baseline HIV RNA <100K Copies/mL

NNRTI	Efavirenz + abacavir/lamivudine Rilpivirine/emtricitabine/tenofovir DF*
PI	Atazanavir + ritonavir + abacavir/lamivudine

*Available as a once-daily, single-tablet regimen.
Notes:
Efavirenz: avoid use in women trying to conceive or are sexually active and not using contraception.
Abacavir: only for patients who are HLA-B*5701 negative.
Lamivudine may substitute for emtricitabine or visa versa.
Tenofovir DF: use with caution in patients with renal insufficiency.
Rilpivirine/emtricitabine/tenofovir DF: only for patients with pre-ART CD4 >200 cells/mm^3.
Atazanavir + RTV: absorption depends on food and low gastric pH.

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

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DHHS Guidelines: Alternative Regimens

May Be the Preferred Regimen for Some Patients

PI	Darunavir + ritonavir + abacavir/lamivudine Lopinavir/r (qd or bid) + abacavir/lamivudine or emtricitabine/tenofovir DF
INSTI	Raltegravir + abacavir/lamivudine

Notes:
Abacavir: only for patients who are HLA-B*5701 negative.
Lamivudine may substitute for emtricitabine or visa versa.

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

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IAS-USA Guidelines: Recommended Regimens

INSTI	Elvitegravir/cobicistat/emtricitabine/tenofovir DF Dolutegravir + emtricitabine/tenofovir DF Dolutegravir + abacavir/lamivudine[1] Raltegravir + emtricitabine/tenofovir DF
NNRTI	Rilpivirine[2]/emtricitabine/tenofovir DF Efavirenz/emtricitabine/tenofovir DF Efavirenz + abacavir/lamivudine[1,3]
PI	Atazanavir + ritonavir + emtricitabine/tenofovir DF Atazanavir + ritonavir + abacavir/lamivudine[1,3] Darunavir + ritonavir (qd) + emtricitabine/tenofovir DF

[1]HLA-B*5701-negative patients. Use with caution in patients with high cardiovascular risk.
[2]Patients with baseline plasma HIV RNA ≤100,000 copies/mL.
[3]Abacavir/lamivudine was less efficacious with baseline HIV-1 RNA level >100,000 copies/mL than emtricitabine/tenofovir DF when these agents were given with efavirenz or ritonavir-boosted atazanavir.

Günthard HF, et al. *JAMA*. 2014;312:410-425.

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IAS-USA Guidelines: Alternative Regimens

INSTI	Raltegravir + abacavir/lamivudine[1]
NNRTI	Nevirapine + 2 NRTIs Rilpivirine[2] + abacavir/lamivudine[1]
PI	Atazanavir/cobicistat[3] + 2 NRTIs Darunavir/cobicistat[3] + 2 NRTIs Darunavir + ritonavir + abacavir/lamivudine[2] Lopinavir/r + 2 NRTIs Darunavir + ritonavir + raltegravir[4] Lopinavir/r + lamivudine Lopinavir/r + raltegravir

[1]HLA-B*5701-negative patients. Use with caution in patients with high cardiovascular risk.
[2]Patients with baseline plasma HIV RNA <100,000 copies/mL.
[3]FDA approval of fixed-dose combination is anticipated in 2014.
[4]Less effective at CD4 <200 cells/µL or possibly HIV RNA >100,000 copies/mL.

Günthard HF, et al. *JAMA*. 2014;312:410-425.

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Recommended Laboratory Tests at ART Initiation and Follow-Up

	ART Initiation	2-8 Weeks Post ART	Repeat Every 3-6 Months	Repeat Every 6 Months	Repeat Every 12 Months	Treatment Failure	Clinically Indicated
CD4	√				*		√
HIV RNA	√	√	√				√
Resistance	√						√
Basic chemistry	√	√	√				√
LFT, bilirubin	√	√	√				√
CBC+differential	√	√ (ZDV)	√				√
Fasting lipids	√	√		√‡	√‡		√
Fasting glucose	√		√‡	√‡			√
Urinalysis	√			√ (HIVAN)	√ (TDF)		√
HLA-B*5701	√ (ABC)						
Pregnancy	√ (EFV)						√
Tropism	√ (CCR5 antagonist)					√ (CCR5 antagonist)	√

*Every 6 to 12 months: on a suppressive regimen and CD4 counts well above the threshold for OI risk.
‡Borderline or abnormal at last measurement; ^normal at last measurement.

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

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Antiretroviral Pregnancy Registry Study (www.APRegistry.com)

- Prospective, international exposure-registration study (1989-2014; n=18,809 pregnancies reported)
  - >80% of cases are from the US
  - CDC population-based birth defects surveillance system
- APR overall findings
  - Overall birth defect rate comparable to CDC population-based surveillance data (2.8% versus 2.72%)
  - No specific birth defect patterns detected
  - Similar rates seen for PIs, NRTIs, and NNRTIs during first trimester exposure

Interim Report June 2014. Available at: www.APRegistry.com.

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Antiretroviral Pregnancy Registry Study (www.APRegistry.com)

	Defects/Live Births (>200 reported 1st trimester exposures)	Prevalence % (95% CI)
NRTIs		
Abacavir	28/925	3.0 (2.0, 4.4)
Didanosine	20/418	4.8 (3.0, 7.3)
Emtricitabine	35/1543	2.3 (1.6, 3.1)
Lamivudine	137/4418	3.1 (2.6, 3.7)
Stavudine	21/809	2.6 (1.6, 4.0)
Tenofovir DF	47/2141	2.2 (1.6, 2.9)
Zidovudine	129/4034	3.2 (2.7, 3.8)
PIs		
Atazanavir	20/922	2.2 (1.3, 3.3)
Indinavir	7/289	2.4 (1.0, 4.9)
Lopinavir	26/1174	2.2 (1.4, 3.2)
Nelfinavir	47/1212	3.9 (2.9, 5.1)
Ritonavir	53/2391	2.2 (1.7, 2.9)
Darunavir	6/258	2.3 (0.9, 5.0)
NNRTIs		
Efavirenz	18/797	2.3 (1.3, 3.5)
Nevirapine	31/1068	2.9 (2.0, 4.1)

Interim Report June 2014. Available at: www.APRegistry.com.

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Special Considerations for Common Comorbidities in HIV

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Special Considerations for Common Comorbidities in HIV

- **Metabolic Considerations**
  - Cardiovascular disease/dyslipidemia
  - Diabetes/insulin resistance
- Cancer
- Sexually transmitted disease
- Hepatitis coinfection

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Screening Recommendations for Metabolic Diseases in All HIV Patients

	Frequency of Assessment
History	
Family history of premature CHD, diabetes, hypertension	At HIV diagnosis
Fasting glucose and/or hemoglobin A1c	At HIV diagnosis, before and within 1-3 months after starting ART, and every 6 months thereafter
Fasting lipid levels	At HIV diagnosis, before and within 1-3 months after starting ART, and per NCEP guidelines thereafter
Baseline bone densitometry (DXA) screening for osteoporosis	Men ≥50 years of age and postmenopausal women

Aberg JA, et al. *Clin Infect Dis.* 2014;58:e1-e34.

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Key Screening and Management Approaches for Common Comorbidities in HIV

- **Metabolic Considerations**
  - **Cardiovascular disease/dyslipidemia**
  - Diabetes/insulin resistance
- Cancer
- Sexually transmitted disease
- Hepatitis coinfection

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Factors That Potentially Impact Cardiovascular Risk in HIV Patients

Increasing Cardiovascular Risk

- **Dyslipidemia, insulin resistance, body habitus changes associated with HIV itself and certain components of HAART**
- **High rates of other cardiovascular risk factors, in particular smoking**
- **Prolongation of survival**
  - **Older patients are intrinsically at greater cardiovascular risk**

Decreasing Cardiovascular Risk

- **Control of HIV RNA replication with HAART improves endothelial function**
- **Current HAART regimens**
  - **More favorable metabolic and morphologic profiles than earlier regimens**
  - **Some regimens reduce inflammatory markers and immune activation**
- **Increased awareness and management of dyslipidemia**

Currier JS, et al. *Circulation.* 2008;118:e29-e35.

59

D:A:D Study: Risk Factors Associated With CVD-Related Mortality in HIV Patients

- **HIV-infected patients (n=33,347)**
  - **Total deaths (n=2482)**
    - **Cardiovascular-related: 11.6%**
  - **Follow-up**
    - **180,176 person-years**
- **Significant risk factors for cardiovascular-related mortality**
  - **Diabetes, hypertension, smoking, age**
  - **Lower CD4 counts were associated with a higher risk of death**
- **Need to address modifiable risk factors to further reduce cardiovascular-related mortality**

	Adjusted Rate Ratios for Cardiovascular Death (95% CI)
Diabetes	1.83 (1.29-2.59)
Hypertension	2.04 (1.57-2.66)
Smoking	1.90 (1.29-2.80)
Age	1.46 (1.38-1.54)

Smith C, et al. *AIDS*. 2010;24:1537-1548.

60

Screening for Cardiovascular Risk Factors

IDSA

- Fasting lipids
  - Before ART and within 1-3 months after starting ART
- Fasting glucose
  - Before and within 1-3 months after starting ART and every 6 months thereafter
- Routine measurements of body weight and patient-reported body shape changes

NY State Department of Health AIDS Institute

- Fasting lipids and glucose
  - Before ART and within 3 to 6 months of starting a new regimen, and annually thereafter
  - Annually for patients not on ART
- Screen for illicit substances or tobacco at baseline and at least annually

Aberg JA, et al. *Clin Infect Dis*. 2014;58:e1-e34.
New York State Department of Health. Available at: http://www.hivguidelines.org/GuideLine.aspx?pageID=257&guideLineID=13.
Hsue PY, et al. *Circulation*. 2008;118:e41-e47.

81

Screening for Coronary Heart Disease

- Complete clinical history
- Physical examination
- Risk assessment with the Framingham Risk Equation (or similar)
  - Every patient without ischemic heart disease
    - Before HAART initiation
    - Annually thereafter
- 12-lead ECG
  - Men (>40 years) and women (>50 years of age)
    - Annually

Hsue PY, et al. *Circulation*. 2008;118:e41-e47.
Lundgren JD, et al. *HIV Med*. 2008;9:72-81.

82

Calculation of 10-Year CHD Risk Using the Framingham Risk Equation

- Incorporates
  - Age
  - Total cholesterol
  - HDL-C
  - Blood pressure
  - Smoking status
- 10-year CHD risk categories
  - Low (<10%)
  - Intermediate (10% to 20%)
  - High (>20%)

hin.nhlbi.nih.gov/atpiii/calculator.asp.

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Prevention of Cardiovascular Disease

Estimate Risk of Cardiovascular Disease

CHD Risk <10%	CHD Risk 10%-20%	CHD Risk >20% Prior CVD, Type 2 Diabetes, Type 1 Diabetes with Microalbuminuria
LDL-C Cut-Off: 190 mg/dL (155 to 190 mg/dL)	LDL-C Cut-Off: 155 mg/dL (115 to 155 mg/dL)	LDL-C Cut-Off: 115 mg/dL (80 to 115 mg/dL)
Consider Modifying ART*	Consider Modifying ART*	Strongly Consider Modifying ART*†

If lifestyle changes, with or without modification of ART, do not result in sufficient lowering of LDL-C to below target level, consider using lipid-lowering medication

*Only if LDL-C is above cut-off level, ART is thought to contribute to the increase in LDL-C, if possible without compromising HIV RNA suppression.
†Patients >20% CVD or prior CVD, the risk of CVD events and cardiac death will usually be higher than the risk of progression to AIDS or death.

Lundgren JD, et al. *HIV Med.* 2008;9:72-81.

54

Dyslipidemia in HIV: Approaches to Consider

- Behavior modification
  - Diet, exercise, smoking cessation
- Pharmacologic therapy
  - Statins and fibrates
  - Second-line lipid-lowering agents
- Drug substitution of offending agents
  - Consider substituting with
    - Tenofovir DF or abacavir for stavudine or zidovudine
    - NNRTI for a PI in NNRTI-naïve patients
    - A different ritonavir-boosted PI for other PIs or NNRTIs

Schambelan M, et al. *JAIDS.* 2002;31:257-275.
Wohl DA, et al. *Clin Infect Dis.* 2006;43:645-653.

55

Prevention of Cardiovascular Disease: Options of ART Modification

- Replace ritonavir-boosted PI with an NNRTI
  - May replace with another ritonavir-boosted PI that is known to cause less metabolic disturbance
- Replace zidovudine or stavudine with tenofovir DF
  - In patients with higher risk for cardiovascular disease, consider switching to tenofovir DF

Lundgren JD, et al. *HIV Med.* 2008;9:72-81.
DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

56

Treatment-Associated Hyperlipidemia: Hierarchy of Risk (Highest to Lowest Risk)

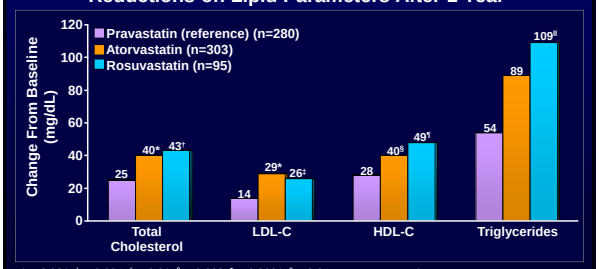
- NRTIs[1-5]
  - Stavudine > zidovudine > abacavir = tenofovir DF
  - Combinations
    - Stavudine + lamivudine > tenofovir DF + lamivudine
    - Zidovudine/lamivudine > emtricitabine/tenofovir DF
    - Stavudine + didanosine > emtricitabine + didanosine
    - Stavudine + didanosine > abacavir + lamivudine
- Ritonavir-boosted PIs[6-10]
  - Indinavir, lopinavir, tipranavir > atazanavir, darunavir, fosamprenavir, saquinavir
  - Ritonavir: full dose > boosting dose
- NNRTIs[11]
  - Efavirenz > nevirapine (both increases HDL-C)

[1]Gallant JE, et al. *JAMA*. 2004;292:191-201; [2]Pozniak AL, et al. *JAIDS*. 2006;43:535-540; [3]Shlay JC, et al. *JAIDS*. 2005;38:147-155; [4]Podzamczer D, et al. *JAIDS*. 2007;44:139-147; [5]Mallon PW, et al. *AIDS*. 2003;17:971-979; [6]Johnson M, et al. *AIDS*. 2005;19:685-694; [7]Smith K, et al. *AIDS Res Ther*. 2008;5:5; [8]Walmsley S, et al. *JAIDS*. 2009;50:367-374; [9]Mills A, et al. *AIDS*. 2009;23:1679-1688; [10]Molina J-M, et al. *JAIDS*. 2010;53:323-332.; [11]van Leth F, et al. *PLOS Med*. 2004;1:64-74.

57

Impact of Statins in Routine Clinical Care of HIV-Infected Patients

Reductions on Lipid Parameters After 1 Year



*P<0.001; †P=0.004; ‡P<0.01; §P=0.002; ¶P=0.0001; #P=0.04 versus pravastatin.

Singh S, et al. *Clin Infect Dis*. 2011;52:387-395.

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Key Screening and Management Approaches for Common Comorbidities in HIV

- Metabolic Considerations
  - Cardiovascular disease/dyslipidemia
  - Diabetes/insulin resistance
- Cancer
- Sexually transmitted disease
- Hepatitis coinfection

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Pathogenic Mechanisms of Insulin Resistance

- Similar in HIV and non-HIV patients
  - Genetic influences
  - Elevated circulating free fatty acids
  - Increased muscle and organ fat
  - Hormones
  - Comorbid diseases
  - Chronic inflammatory changes (cytokines)
- Specific for HIV-infected patients
  - Lipodystrophy
  - HAART components, particularly PIs and some NRTIs (didanosine, stavudine)

Florescu D, et al. *Antiviral Ther.* 2007;12:149-162.

70

Insulin Resistance in HIV Disease

- Increases the risk of cardiovascular disease, either alone or in combination with other factors
- Often associated with a cluster of metabolic abnormalities (metabolic syndrome)
  - Hypertension, hypertriglyceridemia, hypercholesterolemia, low HDL-C levels, and truncal adiposity
- Risk factors for diabetes and insulin resistance
  - Exposure to some PIs and NRTIs
    - PIs: indinavir, lopinavir/r, ritonavir
    - NRTIs: didanosine, stavudine, zidovudine
  - Increasing age
  - Visceral adiposity
  - Dorsocervical fat accumulation
  - Lipoatrophy

Florescu D, et al. *Antivir Ther.* 2007;12:149-162.

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ADA Definitions of Abnormal Glucose Metabolism

	Fasting Plasma Glucose (mg/dL)	Oral Glucose Tolerance Test 2-Hour Post-Load (mg/dL)
Normal	<100	<140
Impaired fasting glucose	100 to 125	--
Impaired glucose tolerance	--	140 to 199
Diabetes (provisional)	≥126	≥200

ADA. *Diabetes Care.* 2008;31(suppl 1):S55-S60.

72

ADA 2011 Criteria for the Diagnosis of Diabetes Mellitus

- A1C ≥6.5%

  OR
- FPG ≥126 mg/dL (7.0 mmol/L)

  OR
- 2-hour plasma glucose >200 mg/dL (11.1 mmol/L) during an OGTT (75-g oral glucose load)

  OR
- Symptoms of hyperglycemia or hyperglycemic crisis or a random plasma glucose ≥200 mg/dL (11.1 mmol/L)

FPG: fasting plasma glucose.
OGTT: oral glucose tolerance test.

American Diabetes Association. *Diabetes Care.* 2011;34(suppl 1):S62-S69.

73

ADA Screening Criteria for Pre-Diabetes or Type 2 Diabetes in Adults

- All adults who are overweight (BMI ≥25 kg/m2) and have additional risk factors
- In the absence of the above criteria, testing for pre-diabetes and diabetes should begin at age 45 years
- If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status

Additional Risk Factors

- Physical inactivity
- First-degree relative with diabetes
- High-risk ethnic population (eg, African American, Latino, Native American, Asian American, and Pacific Islander)
- Women who delivered a baby weighing >9 lb or were diagnosed with GDM
- Hypertension (≥140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL
- Women with polycystic ovarian syndrome
- Impaired glucose tolerance or fasting glucose on previous testing
- Other clinical conditions associated with insulin resistance
- History of cardiovascular disease

ADA. *Diabetes Care.* 2014;37(suppl 1):S14-S80.

74

Recommended Laboratory Tests

- Fasting serum glucose measurement
  - Before starting treatment
    - If normal, annually thereafter
  - 3 to 6 months after starting HAART if borderline or abnormal before starting treatment
    - If normal, repeat every 6 months
- Oral glucose tolerance test
  - In patients with family history of diabetes, obesity or metabolic syndrome, on HAART
    - At the first visit
    - Repeat when there is a clinical suspicion of impaired glucose tolerance

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.
Florescu D, et al. *Antiviral Ther.* 2007;12:149-162.

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ADA Recommendations for the Prevention/Delay of Type 2 Diabetes

- Patients with impaired glucose tolerance or impaired fasting glucose
  - Counsel on weight loss of 5% to 10% of body weight
  - Increase physical activity to at least 150 minutes/week of moderate activity (eg, walking)
- Follow-up counseling appears to be important for success
- In addition to lifestyle counseling, metformin may be considered in those who are at very high risk (combined impaired fasting glucose and impaired glucose tolerance plus other risk factors) and who are obese and <60 years of age
- Monitoring for the development of diabetes in those with pre-diabetes should be performed every year

ADA. *Diabetes Care.* 2014;37(suppl 1):S14-S80.

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Recommended Approaches: Insulin Resistance, Glucose Intolerance, and Diabetes Mellitus in HIV

- Avoid individual PIs and NRTIs (didanosine and stavudine) that are associated with development of insulin resistance
- Lifestyle modification
  - Diabetic education, self-monitoring of blood glucose, aerobic and resistance training
- Metformin
  - Monitor for lactic acidosis during first months of therapy
  - Contraindicated in patients with renal failure
- Thiazolidinediones
  - Monitor liver function every 2 months for first 12 months of therapy
  - Avoid using if AST and ALT are >2.5x the upper limit of normal

Wohl DA, et al. *Clin Infect Dis.* 2006;43:645-653.
Florescu D, et al. *Antivir Ther.* 2007;12:149-162.

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Recommended Approaches: Insulin Resistance, Glucose Intolerance, and Diabetes Mellitus in HIV

- If impaired fasting glucose or diabetes occurs while on therapy, it is reasonable to switch to agents that are less associated with this metabolic complication
- Switching therapy
  - Switch PI-based HAART to NNRTI-based HAART
  - Switch from thymidine NRTI in the presence of diabetes or glucose intolerance

Wohl DA, et al. *Clin Infect Dis.* 2006;43:645-653.
Florescu D, et al. *Antivir Ther.* 2007;12:149-162.

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Key Screening and Management Approaches for Common Comorbidities in HIV

- Metabolic Considerations
  - Cardiovascular disease/dyslipidemia
  - Diabetes/insulin resistance
- **Cancer**
- Sexually transmitted disease
- Hepatitis coinfection

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Malignancies in HIV: Changes in Incidence Over the Past 10 Years

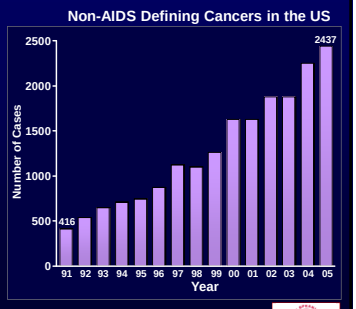
- **AIDS-related malignancies**
  - **Decreased**
    - **Kaposi sarcoma and CNS lymphoma**
  - **Increased**
    - **Non-Hodgkin lymphoma**
- **Non-AIDS defining malignancies**
  - **Overall incidence increased by >3-fold**
  - **Greatest increases seen in liver, larynx, anal, and lung cancers**
  - **No increase in prostate and breast cancers**

Mitsuyasu RT. *Top HIV Med.* 2008;16:117-121.
Engels EA, et al. *Int J Cancer.* 2008;123:187-194.
Patel P, et al. *Ann Intern Med.* 2008;148:728-736.

80

CDC: Non-AIDS-Defining Cancer in the United States Among the HIV-Infected

- **Overall cancer burden in HIV infected from 2004 to 2007* (n=15,885)**
  - **AIDS-defining cancers (49.5%)**
  - **Non-AIDS defining cancers (47.3%)**
  - **Poorly defined cancers (3.2%)**
- **From 1991 to 2005**
  - **AIDS-defining cancers declined from 7289 to 1736 cases**
  - **Non-AIDS defining cancers increased from 416 to 2437 cases**

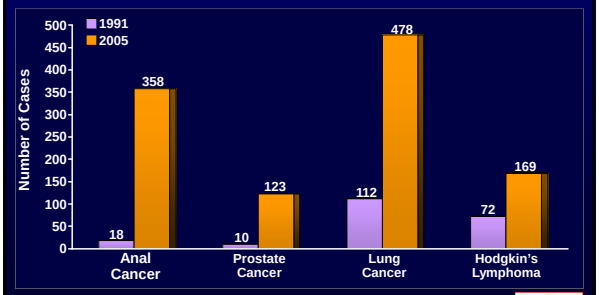


***Data from 34 states.**

Shiels M, et al. *J Natl Cancer Inst.* 2011;103:753-762.

81

CDC: Changes in Non-AIDS-Defining Cancer Among the HIV-Infected



Shiels M, et al. *J Natl Cancer Inst*. 2011;103:753-762.

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Non-AIDS Defining Cancer Risk in HIV Infection

- Risk for cancer overall and for individual malignancies in HIV is difficult to accurately define
  - Absence of relevant or good-quality data
  - Competing risk factors for death
  - Underreporting
  - Variations in screening practices
  - Under diagnosis
  - Population factors

Mitsuyasu RT. *Top HIV Med*. 2008;16:117-121.

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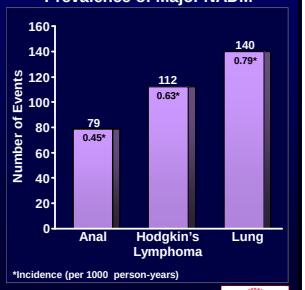
D:A:D Study: Non-AIDS Defining Malignancies

- Prospective cohort (n=41,746; 2004-2010)
  - NADM (n=880): 4.98/1000 person-years (95% CI 4.65-5.31)
- Risk of NADM
  - Increased with low CD4 counts
  - Low nadir CD4 remains associated with a persistent increase in risk
- HIV viremia associated with increased risk for Hodgkin's lymphoma but not anal or lung cancer

Prevalence of Major NADM



NADM: non-AIDS defining malignancies.
Worm SW, et al. *BMC Infect Dis*. 2013;13:471.

84

D:A:D Study: Risk Factors Associated With Non-AIDS Cancer Mortality in HIV Patients

- HIV-infected patients (n=33,347)
  - Total deaths (n=2482)
    - Cancer-related deaths: 11.5%
  - Follow-up
    - 180,176 person-years
- Significant risk factors for non-AIDS cancers mortality
  - Low BMI, smoking, and age
  - Lower CD4 counts were associated with a higher risk of death
- Need to address modifiable risk factors to further reduce non-AIDS cancer mortality

	Adjusted Rate Ratios for Non-AIDS Cancer Death (95% CI)
Low (<18 kg/m^2)	2.03 (1.28-3.21)
Smoking	2.20 (1.48-3.26)
Age	1.47 (1.38-1.54)

Smith C, et al. *AIDS*. 2010;24:1537-1548.

85

NCI and CDC: Excess Burden of Cancer Among HIV Infected in the US (2010)

- Retrospective analysis
  - Expected HIV cancer rates: HIV/AIDS Cancer Match study
  - General population cancer rates: SEER program
- Excess cancer burden in the US HIV population in 2010: 54%
  - Nearly 65% occurred in MSM
  - Largest increase in NHL, Kaposi sarcoma, anal cancer, lung cancer
  - Largest excess occurred in those 40 to 49 years of age
    - Largest percentage excess in those 15 to 29 years of age

Excess or Deficit Cancer Cases Among HIV Infected in the US

	Expected Cancers (number)	Excess or Deficit (%)
NHL (n=1645)	203	87.7
Kaposi sarcoma (n=912)	2	99.8
Lung (n=837)	401	52.0
Anus (n=764)	20	97.4
Prostate (n=574)	969	-40.7
Liver (n=389)	106	72.7
Colorectum (n=357)	379	-5.8
Hodgkin lymphoma (n=317)	29	90.0
Female breast (n=177)	303	-41.6

SEER: Surveillance, Epidemiology, and End Results.

Robbins HA, et al. 21st CROI. Boston, 2014. Abstract 707.

86

NCI: HIV and Cancer-Specific Mortality in the US (1996-2010)

- Retrospective analysis of data from 5 US cancer registries (HIV/AIDS Cancer Match study)
  - Cancer-specific mortality by HIV status
- HIV-infected cancer patients
  - Experienced higher cancer-specific mortality than HIV-uninfected cancer patients for 8 out of 14 cancers
    - Additional 3 cancers (anal, liver, and cervical) had suggested elevations of cancer-specific mortality

Adjusted Hazard Ratios for Cancer-Specific Mortality
(HIV Infected versus Uninfected)

	HR (95% CI)
Oral cavity/pharynx	1.50 (1.07-2.09)
Colon and rectum	1.69 (1.36-2.11)
Pancreas	1.63 (1.26-2.10)
Larynx	1.92 (1.23-2.98)
Lung	1.28 (1.17-1.40)
Melanoma	1.76 (1.10-2.79)
Breast	2.71 (2.10-3.50)
Prostate	1.83 (1.16-2.87)

Adjusted for age, sex, year of diagnosis, and cancer stage at presentation.

Coghill AE, et al. 21st CROI. Boston, 2014. Abstract 99.

87

Prevention

- Smoking cessation
- Use of hepatitis and HPV vaccines in seronegative individuals
  - Immunogenicity studies for HPV underway in HIV-infected persons
- Maintain a high suspicion for cancer in HIV-infected persons

Mitsuyasu RT. *Top HIV Med*. 2008;16:117-121.

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Early Detection and Prevention

- Yearly intervals
  - Cervical and anal Papanicolaou tests
  - Gynecologic examinations and high-resolution anoscopy
  - Breast examinations
  - Prostate examinations (including prostate-specific antigen)
- Periodically
  - Liver function tests and alpha-fetoprotein in HBV and/or HCV coinfection
- Sunscreen and avoidance of overexposure to sunlight
  - Endothelial and epithelial cells in HIV-infected patient may be more susceptible to carcinogenesis

Mitsuyasu RT. *Top HIV Med*. 2008;16:117-121.

89

MD Anderson Cancer Center: ART Use in HIV Patients With Cancer

- Retrospective analysis of HIV-positive patients with cancer or hematopoietic stem cell transplantation (2001-2012)
  - HIV treatment initiated or monitored by MD Anderson ID group
- ART efficacy
  - Absence of virologic failure (HIV RNA >200 copies/mL) for ≥6 months or HIV RNA rebound after suppression (HIV RNA <200 copies/mL)
- Endpoints
  - Primary: safety and tolerability
  - Secondary: ART efficacy

Baseline by ART (all patients received NRTIs)

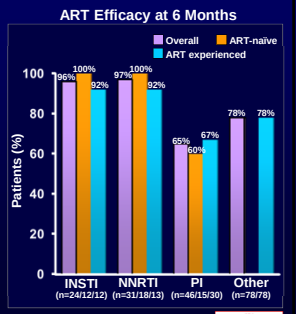
	INSTI (n=30)	PI (n=57)	NNRTI (n=50)	Other (n=17)
Age (years)	51	50	48	53
Male (%)	80	74	82	94
Race (%)				
White/black	63/27	53/37	44/30	47/35
Type of cancer (%)				
Hematologic	83	42	68	41
NHL	68	79	71	57
Solid tumor	17	58	32	59
Gastrointestinal	40	33	25	30
ART status at cancer diagnosis (%)				
Naïve	50	33	46	0
Experienced	50	67	54	100

Torres HA, et al. *Clin Microbiol Infect*. 2014;February 16. [Epub ahead of print].

90

MD Anderson Cancer Center: Efficacy and Safety of ART in Cancer

- INSTIs were most commonly used in patients concomitantly receiving
  - High-dose steroids, topoisomerase inhibitors, alkylating agents, or antimetabolites
- INSTI or NNRTI-based ART resulted in increased efficacy and safety without causing significant adverse effects
- INSTI appear to be preferred when interactions with chemotherapeutic and antifungal agents are anticipated



All patients received NRTIs.

Torres HA, et al. *Clin Microbiol Infect*. 2014;February 16. [Epub ahead of print].

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Key Screening and Management Approaches for Common Comorbidities in HIV

- Metabolic Considerations
  - Cardiovascular disease/dyslipidemia
  - Diabetes/insulin resistance
- Cancer
- **Sexually transmitted disease**
- Hepatitis coinfection

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Screening Strategies to Detect Asymptomatic STDs: First Visit

- All patients
  - Serologic test for syphilis
    - RPR or VDRL, confirm positive test with FTA-Abs or TP-PA
  - Consider testing for gonorrhea, *Chlamydia* species, and herpes simplex based on patient sexual history
  - Serologic tests for hepatitis A, B, C at baseline
- Female
  - Culture or DNA amplification test for gonorrhea
  - Urine sample examination for *Trichomonas* infection
  - Immunofluorescence or DNA amplification for chlamydia if:
    - Sexually active (≤25 years of age)
    - At increased risk for particular situation (eg, commercial sex worker)

Aberg JA, et al. *Clin Infect Dis.* 2014;58:e1-e34.
New York State Department of Health. Available at:
http://www.hivguidelines.org/GuideLine.aspx?pageID=257&guideLineID=13.

93

Screening Strategies to Detect Asymptomatic STDs: Subsequent Visits

- All sexually active patients
  - Screening tests for STDs should be repeated at least annually
- More frequent periodic screening (at least 3 to 6 month intervals) for asymptomatic persons at higher risk
  - Multiple or anonymous sex partners
  - Past history of any STD
  - Behaviors associated with transmission of HIV or other STDs
  - Sexual or needle-sharing partners with any of the above risks
  - Changes in lifestyle/circumstances that are associated with increased risk behavior
  - High prevalence of STDs in the area or in the patient population

Aberg JA, et al. *Clin Infect Dis.* 2014;58:e1-e34.
New York State Department of Health. Available at: http://www.hivguidelines.org/GuideLine.aspx?pageID=257&guideLineID=13.

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Key Screening and Management Approaches for Common Comorbidities in HIV

- Metabolic Considerations
  - Cardiovascular disease/dyslipidemia
  - Diabetes/insulin resistance
- Cancer
- Sexually transmitted disease
- Hepatitis coinfection

95

HIV/HBV-Coinfection: Management Begins With Detection

- All HIV-infected patients should be screened for HBV (anti-HBs and HBsAg)
- Vaccination should be offered to anti-HBV-negative patients
- Response to vaccine is influenced by CD4 count and HIV RNA level
  - Initiate HAART first if CD4 count is <200 cells/mm^3 and there is ongoing HIV RNA replication

HBsAg	Anti-HBs	Meaning	Action
Negative	Negative	Susceptible	Vaccinate
Negative	Positive	Immune, previous infection or vaccination	None
Positive	Negative	Chronic (or acute) hepatitis B infection	HBeAg HBV DNA, Repeat in 6 months if suspect acute HBV

USPHS Guideline. Available at: http://www.cdc.gov/ncidod/diseases/hepatitis/b/Bserology.htm.
Lok AS, et al. Hepatology. 2009;50:661-662. Available at: http://www.aasld.org/Pages/Default.aspx.
EASL. *J Hepatol*. 2009;50:227-242.

96

Immunologic Markers of HBV Infection

	Acute HBV	Recovery From Acute HBV	Chronic HBV Disease: HBeAg Positive	Chronic HBV Disease: HBeAg Negative	Chronic HBV Disease: Inactive HBeAg Carrier State
HBsAg	✓ (may clear)		✓	✓	✓
Anti-HBs		✓			
Anti-HBc IgM	✓				
Anti-HBc	✓	✓	✓	✓	✓
HBeAg	✓		✓		
Anti-HBe		✓ (in some cases)		✓	✓

Hadziyannis SJ, et al. *MedGenMed.* 2003;5(4):1.

97

HIV/HBV-Coinfected Patients

- Advise to abstain from alcohol
- Should receive hepatitis A vaccine if found not to be immune at baseline
  - Absence of hepatitis A total or IgG antibody
- Advise on methods to prevent HBV transmission (similar to those used to prevent HIV transmission)
- Evaluate for the severity of HBV infection

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

98

Baseline Evaluation of Patients for Chronic HBV

- History and physical examination
- Laboratory tests
  - CBC with platelets, liver panel, INR
  - HBV DNA
  - HBV genotype (eg, A, B, C, D, etc)
  - HBeAg and anti-HBe
  - Anti-HAV, anti-HCV, anti-HDV (in endemic areas and injection drug users)
  - Alpha-fetoprotein and ultrasound in high-risk
  - Liver biopsy or non-invasive evaluation to grade and stage disease (as needed)

Lok AS, et al. *Hepatology.* 2009;50:661-662. Available at: http://www.aasld.org/Pages/Default.aspx.
Keeffe EB, et al. *Clin Gastroenterol Hepatol.* 2008;6:1315-1341.

99

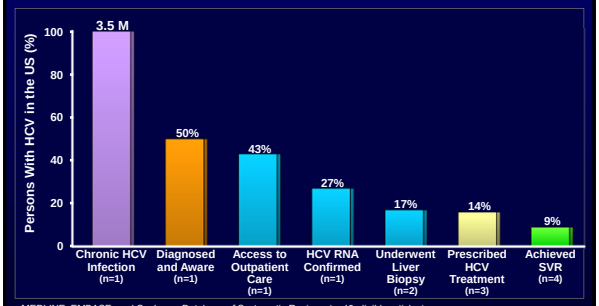
HBV Treatment Options in HIV/HBV-Coinfected Patients

	Preferred	Other Options	Comments
HIV and HBV need treatment			
HBV treatment-naïve	Tenofovir DF/emtricitabine Tenofovir DF + lamivudine	Entecavir + HAART	Avoid single-agent HBV therapy with 3TC, FTC, or TDF due to the increased risk of HBV resistance Other options with limited data in HIV/HBV-coinfection: peginterferon alfa 2a alone; adefovir + (3TC, FTC, or telbivudine) + HAART
Lamivudine resistant	Tenofovir DF/emtricitabine Tenofovir DF + entecavir		Emtricitabine not active against lamivudine-resistant HBV
HBV only needs treatment	Peginterferon 2a Adefovir	Adefovir + telbivudine (monitor HBV DNA at week 24)	Initiate HAART Monitor HBV DNA Monitor liver function

Lok AS, et al. *Hepatology.* 2009;50:661-662. Available at: http://www.aasld.org/Pages/Default.aspx.
DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

100

Chronic HCV Treatment Cascade in the US: Systematic Review and Meta-Analysis (2003-2009)



MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews (n=10 eligible articles).
Numbers in parentheses are number of articles assessing a step in the cascade.
Yehia BR, et al. 21st CROI. Boston, 2014. Abstract 669.

101

DHHS and AASLD Recommendations Prior to ART: HIV/HCV-Coinfected Patients

- HCV antibody (EIA)
  - Performed in all HIV-infected persons
- HCV RNA testing
  - Performed to confirm HCV infection in HIV-infected persons who are positive for anti-HCV
    - If HCV RNA is detected, testing for HCV genotype is recommended to guide selection of the most appropriate antiviral regimen
  - Performed in those who are negative and have evidence of unexplained liver disease
- Patients with HIV/HCV coinfection
  - Advise to avoid alcohol
  - Use appropriate precautions to avoid transmission of both viruses
  - Receive HAV and HBV vaccines if susceptible

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.
AASLD and IDSA. http://www.hcvguidelines.org/full-report-view. Version January 29, 2014.

102

Recommended Pre-Treatment Assessments in HIV/HCV-Coinfected Patients

- Liver disease status
  - HCV RNA, HCV genotype, AFP* and US for HCC, HBV status (HBsAg, anti-HBc), anti-HAV IgG, MELD calculation
- HIV disease status
  - Presence or history of OIs, HIV-associated malignancy, CD4 cell count, HIV RNA, details of HAART
- Factors precluding HCV therapy or requiring control prior to initiating HCV therapy
  - TSH; screen for depression or other psychiatric disease; CBC; blood sugar; history of significant cardiac, renal, or pulmonary disease; fundus examination; beta HCG (women of childbearing potential); social support; treatment adherence

*Most hepatologists recommend; not recommended by AASLD.

Singal AK, et al. *World J Gastroenterol.* 2009;15:3713-3724.

103

Cascade of Care Among HIV Patients Following Diagnosis of HCV Infection

- Retrospective, single-cohort analysis (2008-2012)
  - HIV patients with access to HIV care and HCV antibody positive (n=748)
    - Referred for HCV treatment: 54%
    - Decided to initiate therapy: 44%
    - Actually initiated therapy: 16%
    - Achieved SVR: 7%
- Most important predictor of non-referral for HCV therapy was not being engaged in care
- Ongoing barriers to care prevent many from gaining benefit from IFN-free HCV regimens

Reasons for Not Initiating HCV Treatment After Clinical Staging

	Patients (n=195)
Ongoing barriers to care (%)	40
Prefer IFN-free regimen (%)	23
End-stage liver disease (%)	18
Prior null responder (%)	8
Undetectable HCV RNA level (%)	8
Severe medical comorbidity (%)	3

Cachay ER, et al. 21st CROI. Boston, 2014. Abstract 672.

104

HIV/HCV Coinfection: Who to Treat

- All HCV/HIV coinfected patients are candidates for HCV therapy
- Consider comorbid conditions that limit life expectancy or increase the risks associated with HCV therapy
- HIV disease should be stable with or without ART
- IFN-based regimens
  - Defer HCV treatment if CD4 <200 cells/mm^3
  - Interferon can exacerbate pre-existing mental illness
    - Evaluate patients with underlying psychiatric disease before initiating HCV treatment
- Decompensated cirrhosis
  - Refer to medical practitioner with expertise
- Substance abuse
  - Active substance abuse is not a contraindication
  - Associated with high rates of treatment nonadherence and may compromise treatment outcomes

AASLD and IDSA. Available at: http://www.hcvguidelines.org/full-report-view. Version January 29, 2014.

Sulkowski MS, et al. *J Viral Hepatitis.* 2007;14:371-386.

105

AASLD and IDSA Guidelines: Preferred HCV Regimens in HCV/HIV Coinfection

Genotype 1	
HCV treatment-naïve and prior PR relapsers	
IFN eligible	Sofosbuvir + PR 12 weeks
IFN ineligible	Sofosbuvir + RBV 24 weeks
	Sofosbuvir + simeprevir† ± RBV 12 weeks
HCV treatment experienced*	Sofosbuvir + simeprevir† ± RBV 12 weeks
Genotype 2	
Regardless of HCV treatment history	Sofosbuvir + RBV 12 weeks
Genotype 3	
Regardless of HCV treatment history	Sofosbuvir + RBV 24 weeks
Genotype 4	
Regardless of HCV treatment history	
IFN eligible	Sofosbuvir + PR 12 weeks
IFN ineligible	Sofosbuvir + RBV 24 weeks
Genotype 5 or 6	
Regardless of HCV treatment history	Sofosbuvir + PR 12 weeks

*Prior PR non-responders regardless of IFN eligibility.
†For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if present.
Allowable ART: Sofosbuvir: all except the NRTIs didanosine and zidovudine.
Simeprevir: INSTI (raltegravir); NNRTI (rilpivirine); Entry/Fusion Inhibitor (maraviroc, enfuvirtide); NRTIs (tenofovir, emtricitabine, lamivudine, abacavir).

AASLD and IDSA. Available at: http://www.hcvguidelines.org/full-report-view. Version January 29, 2014.

106

AASLD and IDSA Guidelines: Alternative HCV Regimens in HCV/HIV Coinfection

Genotype 1	
HCV treatment-naïve and prior PR relapsers	
IFN eligible	Simeprevir† 12 weeks + PR 24 weeks
IFN ineligible	None
HCV treatment experienced*	
IFN eligible	Sofosbuvir + PR 12 weeks
IFN ineligible	Sofosbuvir + RBV 24 weeks
Genotype 2 or 3	
HCV treatment-naïve and prior PR relapsers	None
HCV treatment experienced*	
IFN eligible	Sofosbuvir + PR 12 weeks
IFN ineligible	None
Genotype 4, 5, or 6	None

*Prior PR non-responders.
†For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if present.
Allowable ART: Sofosbuvir: all except the NRTIs didanosine and zidovudine.
Simeprevir: INSTI (raltegravir); NNRTI (rilpivirine); Entry/Fusion Inhibitor (maraviroc, enfuvirtide); NRTIs (tenofovir, emtricitabine, lamivudine, abacavir).

AASLD and IDSA. Available at: http://www.hcvguidelines.org/full-report-view. Version January 29, 2014.

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AASLD and IDSA Guidelines: HCV Regimens Not Recommended in HCV/HIV Coinfection

Genotype 1
- Telaprevir + PR 24 or 48 weeks (RGT)
- Boceprevir + PR 28 or 48 weeks (RGT)
- PR 48 weeks
- Simeprevir 12 weeks + PR 48 weeks

Genotype 2 or 3
- Any regimen with telaprevir, boceprevir, or simeprevir
- PR 24 to 48 weeks

Genotype 4, 5, or 6
- Any regimen with telaprevir, boceprevir, or simeprevir
- PR 48 weeks

AASLD and IDSA. Available at: http://www.hcvguidelines.org/full-report-view. Version January 29, 2014.

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Electronic Evaluation Process

- You will receive an electronic evaluation to the email address provided <u>within 1 business day</u>
- Reminder email communications will be sent up to 5 days post lecture until the evaluation is completed
- <u>Completion Is Required</u> for CME/CNE/CPE credit and future attendance
- Incomplete evaluations will preclude attendees from receiving their CME/CNE/CPE certificate & future communications about lectures in your area

Outcomes Measurement Reminder

- We are required to assess "changes in learners' competence, performance or patient outcomes achieved as a result of their participation in a CME/CNE/CPE sponsored educational activity"
- As a result of this requirement you will receive a short survey via email 8 to 12 weeks after completing this course
  - We consider the survey to be an additional component of your overall participation in this educational activity and would urge you to reflect on what you learned in the activity and then complete this survey