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Initiating HAART in the Newly Infected Adolescent

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OBJECTIVES

- Discuss the guidelines and their applicability to adolescents.
- Present an approach to the medical decision-making for initiating ARV therapy.
- Consider the different issues unique to adolescents relative to initiating ARV therapy.
- Demonstrate the application of these considerations with a couple of case-based scenarios.



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The HIV-Infected Adolescent

- Heterogeneous group in numerous respects
- Most acquired HIV behaviorally
 - Many with recent HIV infection
- Some infected perinatally (late presenters)
- Adult guidelines and dosing schedules for ART usually appropriate for post-pubertal adolescents
- Dosing should be based on Tanner stages



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The HIV-Infected Adolescent

Special Considerations:

- Preventing (and screening for) STDs (including HPV)
- Family planning counseling
- For females, gynecologic care, contraception (including interactions with ARVs); avoid EFV
- Prevention of HIV transmission



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The HIV-Infected Adolescent

Challenges to adherence:

- Denial and fear of HIV infection
- Misinformation
- Distrust of the medical establishment
- Fear and lack of belief in the effectiveness of medications
- Low self-esteem
- Unstructured and chaotic lifestyles
- Lack of familial and social support
- Unavailable or inconsistent access to care



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Adherence

- High adherence rates are associated with virologic suppression, low rates of resistance, and improved survival
- Important to assess readiness for ART prior to initiating therapy, and to assess adherence at each clinic visit
- Suboptimal adherence is common



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Measurement of Adherence

- **No gold standard**
- **Patient self-report overestimates adherence, but is associated with viral load responses and is most useful method in the clinic setting**
 - Self-report of suboptimal adherence is strong indicator of non adherence



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Predictors of Good Adherence

- Emotional and practical supports
- Convenience of regimen
- Understanding of the importance of adherence
- Belief in efficacy of medications
- Feeling comfortable taking medications in front of others
- Keeping clinic appointments
- Severity of symptoms or illness



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Predictors of Inadequate Adherence

- Regimen complexity and pill burden
- Low literacy level
- Active drug use or alcoholism
- Mental illness (especially depression)
- Cognitive impairment
- Lack of patient education
- Medication adverse effects
- Treatment fatigue



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Improving Adherence

- Establish readiness to start therapy
- Provide education on medication dosing
- Review potential side effects
- Anticipate and treat side effects
- Use educational aids including pictures, pillboxes, and calendars
- Simplify regimens, dosing, and food requirements
- Engage family, friends
- Utilize team approach with nurses, pharmacists, and peer counselors
- Provide accessible, trusting health care team



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Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Developed by the Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents

A Working Group of the Office of AIDS Research Advisory Council(OARAC)



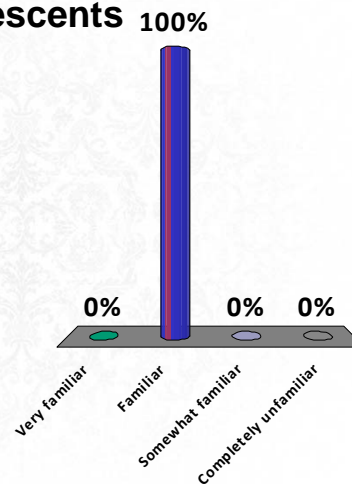
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How familiar are you with the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

1. Very familiar
2. Familiar
3. Somewhat familiar
4. Completely unfamiliar



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Goals of 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



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Patient No. 1

- Danny is a 19 year old, MSM referred to your clinic after testing positive for HIV after donating blood
- No significant past medical history



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Patient No. 2

- **“Mary”** is a 14 yo Haitian female referred to your HIV clinic for medical care.
- She recently immigrated from Haiti and supposedly has perinatal HIV infection but you do not have any records
- **Past Medical History:**
 - Recurrent otitis media
 - Tonsillar/adenoidal hypertrophy with obstructive sleep apnea

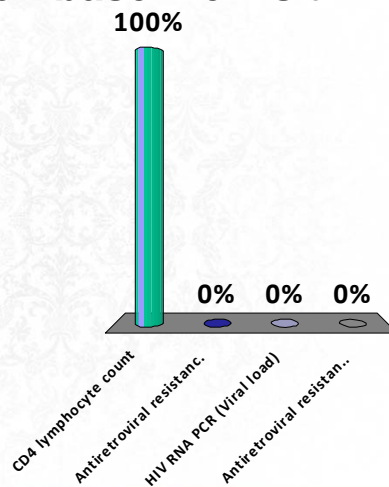


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Which of the following tests is not indicated in these patients at their baseline visit?

1. CD4 lymphocyte count
2. Antiretroviral resistance by phenotype
3. HIV RNA PCR (Viral load)
4. Antiretroviral resistance by genotype



Use of CD4 Cell Levels to Guide Therapy Decisions

- **CD4 count**
 - Major indicator of immune function
 - Most recent CD4 count is best predictor of disease progression
 - A key factor in decision to start ART or OI prophylaxis
 - Important in determining response to ART
 - Adequate response: CD4 increase 50-150 cells/ μ L per year
- **CD4 monitoring**
 - Check at baseline (x 2) and at least every 3-6 months*

* May consider every 6-12 months in clinically stable patients with sustained HIV RNA suppression and CD4 status well above threshold for opportunistic infection risk

Use of HIV RNA Levels to Guide Therapy Decisions

- **HIV RNA**
 - May influence decision to start ART and help determine frequency of CD4 monitoring
 - Critical in determining response to ART
 - Goal of ART: HIV RNA below limit of detection (ie, <20-75 copies/mL, depending on assay)
 - Viral failure is defined as > 200 HIV RNA copies/ml



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Use of HIV RNA Levels to Guide Therapy Decisions

- **RNA monitoring**
 - Check at baseline (x 2)
 - Immediately before initiating ART
 - 2-4 weeks (not more than 8 weeks) after start or change of ART, then every 4-8 weeks until suppressed to <200 copies/mL
 - Every 3-4 months with stable patients; may consider every 6 months for stable adherent patients with VL suppression >2-3 years
 - Isolated “blips” may occur (transient low-level RNA, typically <400 copies/mL), are not thought to predict virologic failure



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Testing for Drug Resistance

- **Before initiation of ART:**
 - Transmitted resistance in 6 -16% of HIV-infected patients
 - In absence of therapy, resistance mutations may decline over time and become undetectable by current assays, but may persist and cause treatment failure when ART is started
 - Identification of resistance mutations may optimize treatment outcomes
 - Resistance testing (genotype) recommended for **all at entry to care**
 - Recommended for **all pregnant women**



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Other Assessment and Monitoring Studies

- **HLA-B*5701 screening**
 - Recommended before starting ABC, to reduce risk of hypersensitivity reaction (HSR)
 - HLA-B*5701-positive patients should not receive ABC
 - Positive status should be recorded as an ABC allergy
 - If HLA-B*5701 testing is not available, ABC may be initiated after counseling and with appropriate monitoring for HSR
- **Coreceptor tropism assay**
 - Should be performed when a CCR5 antagonist is being considered
 - Requires plasma HIV RNA $\geq 1,000$ copies/mL
 - Proviral DNA assay is available for use in samples with HIV RNA below limit of detection; not clinically validated
 - Consider in patients with virologic failure on a CCR5 antagonist (though does not rule out resistance to CCR5 antagonist)



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“Danny”

- Initial CD4 count was:
 - 31% and absolute count of 503
- Viral load was 195 HIV RNA copies/ml
- Viral load was too low to perform resistance testing



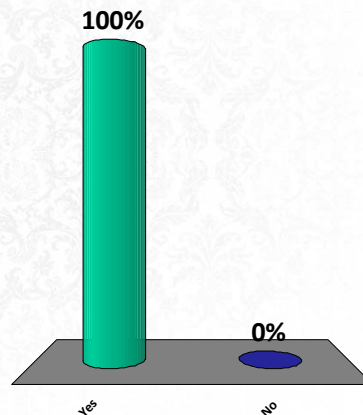
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Would you start antiretroviral therapy for Danny?

1. Yes
2. No



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“Mary”

- Initial CD4 count was:
 - 15% and absolute count of 616
- Viral load was 51,280 HIV RNA copies/ml
- No evidence of resistance by genotype



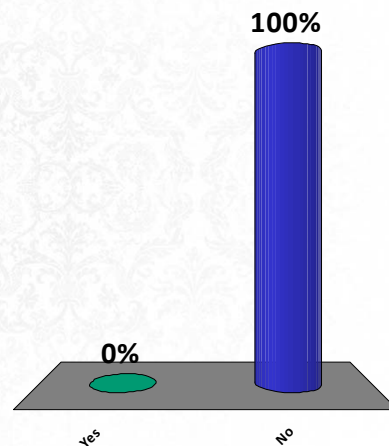
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Would you start antiretroviral therapy for Mary?

1. Yes
2. No



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When to Start ART

- **Potent ART may improve and preserve immune function in most patients with virologic suppression, regardless of baseline CD4 count**
 - ART indicated for all with low CD4 count or symptoms
 - Earlier ART may result in better immunologic responses and better clinical outcomes
 - Reduction in AIDS- and non-AIDS-associated morbidity and mortality
 - Reduction in HIV-associated inflammation and associated complications
 - Reduction in HIV transmission
 - Recommended ARV combinations are considered to be durable and tolerable



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When to Start ART

- Exact CD4 count at which to initiate therapy not known, but evidence points to starting at higher counts
- Current recommendation: ART for all patients with CD4 count of <500 cells/ μ L
 - Randomized control trial (RTC) data support benefit of ART if CD4 count \leq 350 cells/ μ L
 - No RTC data on benefit of ART at CD4 counts of >350 cells/ μ L, but observational cohort data exist
 - For patients with CD4 count >500 cells/ μ L, 50% of the panel recommend ART, 50% consider ART to be optional
- Currently available ARVs are effective and well tolerated



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Potential Benefits of Early Therapy (CD4 count >500 cells/ μ L)

- Cohort study data show survival benefit if ART initiated at CD4 count >500 cells/ μ L
- Earlier ART may prevent HIV-related end organ damage; deferred ART may not reliably repair damage acquired earlier
 - Increasing evidence of direct HIV effects on various end organs and indirect effects via HIV-associated inflammation
- Prevention of sexual and bloodborne transmission of HIV
- Potential decrease in risk of many complications



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Potential Limitations of Early Therapy (CD4 count >500 cells/ μ L)

- ARV-related toxicities
- Non-adherence to ART
- Drug resistance
- Cost



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Recommendations for Initiating ART

Clinical Category or CD4 Count	Recommendation
<ul style="list-style-type: none"> •History of AIDS-defining illness •CD4 count <500 cells/μL •Pregnant women •HIV-associated nephropathy (HIVAN) •Hepatitis B (HBV) coinfection, when HBV treatment is indicated* 	<p>Initiate ART</p>

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



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Recommendations for Initiating ART

- “Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence.”
- Patients may choose to postpone ART
- Providers may elect to defer ART, based on patients’ clinical or psychosocial factors



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Consider More Rapid Initiation of ART

- **Pregnancy**
- **AIDS-defining condition**
- **Acute opportunistic infection**
- **Lower CD4 count (eg, <200 cells/ μ L)**
- **Rapid decline in CD4**
- **Higher viral load**
- **HIVAN**
- **HBV coinfection when HBV treatment is indicated**



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Consider Deferral of ART

- Clinical or personal factors may support deferral of ART
 - If CD4 count is low, deferral should be considered only in unusual situations, and with close follow-up
- When there are significant barriers to adherence
- If comorbidities complicate or prohibit ART
- “Elite controllers” and long-term nonprogressors



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Current ARV Medications

NRTI

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

NNRTI

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

PI

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

Integrase Inhibitor (II)

- Raltegravir (RAL)

Fusion Inhibitor

- Enfuvirtide (ENF, T-20)

CCR5 Antagonist

- Maraviroc (MVC)



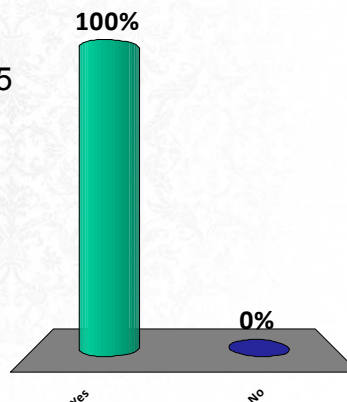
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Would you start ART at this point?

- 6 months later, Danny's CD4 counts are: 26% and 457 with a viral load of 793
- One month later his CD4 counts are: 28% and 393 with a viral load of 1355

1. Yes
2. No



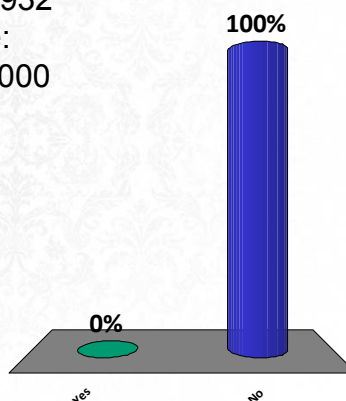
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Would you start ART at this point?

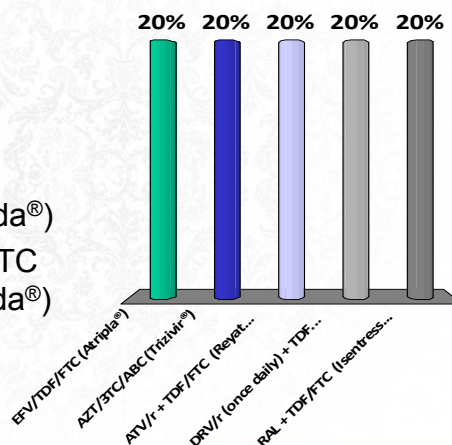
- 3 months later, Mary's CD4 counts are:
13% and 566 with a viral load of 236,932
- One month later her CD4 counts are:
15% and 383 with a viral load of 114,000

1. Yes
2. No



Which of the following antiretroviral regimens is NOT a “preferred” initial treatment regimen?

1. EFV/TDF/FTC (Atripla®)
2. AZT/3TC/ABC (Trizivir®)
3. ATV/r + TDF/FTC (Reyataz®/ritonavir + Truvada®)
4. DRV/r (once daily) + TDF/FTC (Prezista®/ritonavir + Truvada®)
5. RAL + TDF/FTC (Isentress® + Truvada®)



Initial ART Regimens: DHHS Categories

- **Preferred**
 - Randomized controlled trials show optimal efficacy and durability
 - Favorable tolerability and toxicity profiles
- **Alternative**
 - Effective but have potential disadvantages
 - May be the preferred regimen in individual patients
- **Acceptable**
 - Less virologic efficacy, lack of efficacy data, or greater toxicities
- **May be acceptable but more definitive data are needed**



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Initial Treatment: Choosing Regimens

- **3 main categories:**
 - 1 NNRTI + 2 NRTIs
 - 1 PI + 2 NRTIs
 - 1 II + 2 NRTIs
- **Combination of NNRTI, PI, or II + 2 NRTIs preferred for most patients**
- **Fusion inhibitor and CCR5 antagonist not recommended in initial ART**
- **Few clinical end points to guide choices**
- **Advantages and disadvantages to each type of regimen**
- **Individualize regimen choice**



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Initial Treatment: Preferred

NNRTI based	•EFV/TDF/FTC ^{1,2}
PI based	•ATV/r + TDF/FTC ² •DRV/r (once daily) + TDF/FTC ²
II based	•RAL + TDF/FTC ²
Pregnant women	•LPV/r (BID) + 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.



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Initial Treatment: Alternatives

NNRTI based	•EFV ¹ + (ABC/3TC) ^{2,3} or (ZDV/3TC) ² •NVP ⁴ + ZDV/3TC ²
PI based	•ATV/r + (ABC/3TC) ^{2,3} or (ZDV/3TC) ² •FPV/r (daily or BID) + (ABC/3TC) ^{2,3} or (ZDV/3TC) ² or (TDF/FTC) ² •LPV/r (daily or BID) ⁵ + (ABC/3TC) ^{2,3} or (ZDV/3TC) ² or (TDF/FTC) 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.
3. ABC should not be used in patients who test positive for HLA B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
4. NVP should not be started if pre-ARV CD4 >250 in women or >400 in men.
5. Once daily LPV/r is not recommended in pregnant women.



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Initial Treatment: Acceptable

NNRTI based	•EFV ¹ + ddl + (3TC or FTC)
PI based	•ATV ⁴ + (ABC/3TC) ^{2,3} or (ZDV/3TC) ²
CCR5 Antagonist based	•MVC ⁵ + 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.
3. ABC should not be used in patients who test positive for HLA-B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
4. ATV/r generally preferred over ATV; consider unboosted ATV if RTV boosting not possible.
5. Tropism testing required before treatment with MVC; use only if CCR5-tropic virus is present.



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Initial Treatment: May Be Acceptable But More Definitive Data Needed

PI based	•DRV/r + (ABC/3TC) ^{1,2} or (ZDV/3TC) ²
II based	•RAL + (ABC/3TC) ^{1,2} or (ZDV/3TC) ²
CCR5 Antagonist based	•MVC ³ + TDF/FTC ² or ABC/3TC ^{1,2}

1. 3TC can be used in place of FTC and vice versa.
2. ABC should not be used in patients who test positive for HLA-B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
3. Test tropism before treatment with MVC, use MVC only in those with exclusively CCR5-tropic virus.



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Components in Initial Therapy: PIs

ADVANTAGES:

- Higher genetic barrier to resistance
- PI resistance uncommon with failure (boosted PI)
- NNRTIs and II preserved for future use

DISADVANTAGES:

- Metabolic complications (fat maldistribution, dyslipidemia, insulin resistance)
- GI intolerance
- Potential for drug interactions (CYP450), especially with RTV

Components in Initial Therapy: NNRTIs

ADVANTAGES:

- Long half-lives
- Less metabolic toxicity (dyslipidemia, insulin resistance) than with some PIs
- PIs and II preserved for future use

DISADVANTAGES:

- Low genetic barrier to resistance – single mutation
- Cross-resistance among most NNRTIs
- Rash; hepatotoxicity (NVP)
- Potential drug interactions (CYP450)
- Transmitted resistance to NNRTIs more common than resistance to PIs

Components in Initial Therapy: Raltegravir

ADVANTAGES:

- Virologic response noninferior to EFV
- Fewer adverse events than with EFV
- Fewer drug-drug interactions than with PIs or NNRTIs
- NNRTIs and PIs preserved for future use

DISADVANTAGES:

- Less experience with IIs, limited data
- Twice-daily dosing
- Lower genetic barrier to resistance than PIs
- No data with NRTIs other than TDF/FTC in initial therapy



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Components in Initial Therapy: CCR5 Antagonist - Maraviroc

ADVANTAGES:

- Virologic response noninferior to EFV (post hoc analysis)
- Fewer adverse events than with EFV
- NNRTIs and PIs preserved for future use

DISADVANTAGES:

- Requires tropism testing before use
- Less experience than with boosted PI- or NNRTI-based ART
- Limited data with NRTIs other than ZDV/3TC
- Twice-daily dosing
- CYP 3A4 substrate; dosage adjustment required if concomitant inducers or inhibitors



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Components in Initial Therapy: Dual-NRTI Pairs

ADVANTAGES:

- Established backbone of combination therapy
- Minimal drug interactions

DISADVANTAGES:

- Lactic acidosis and hepatic steatosis reported with most NRTIs (rare) (highest incidence with d4T, then ddl and ZDV, lower with TDF, ABC, 3TC, and FTC)
- Lipodystrophy (d4T)
- Renal toxicity and bone toxicity with TDF

Adverse Effects: NRTIs

- **ABC**
 - HSR*
 - Rash
 - Possible increased risk of MI
- **TDF**
 - Renal impairment
 - Decrease in bone mineral density
 - Headache
 - GI intolerance
- **ZDV**
 - Headache
 - GI intolerance
 - Lipodystrophy
 - Bone marrow suppression

* Screen for HLA-B*5701 before treatment with ABC; ABC should not be given to patients who test positive for HLA-B*5701.

Adverse Effects: NNRTIs

- **EFV**
 - Neuropsychiatric (nightmares, sleep disturbances)
 - Teratogenic in nonhuman primates + cases of neural tube defects in human infants after first trimester exposure
 - Dyslipidemia
- **NVP**
 - Higher rate of rash
 - Hepatotoxicity (may be severe and life-threatening; risk higher in patients with higher CD4 counts at the time they start NVP, and in women)



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Adverse Effects: PIs

- **All PIs:**
 - Hyperlipidemia
 - Lipodystrophy
 - Hepatotoxicity
 - GI intolerance
 - Possibility of increased bleeding risk for hemophiliacs
 - Drug-drug interactions



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Adverse Effects: PIs

- **Atazanavir:**
 - Hyperbilirubinemia
 - PR prolongation
 - Nephrolithiasis
- **Darunavir:**
 - Rash
 - Liver toxicity
- **Fosamprenavir:**
 - GI intolerance
 - Rash
 - Possible increased risk of MI
- **Lopinavir/ritonavir:**
 - GI intolerance
 - Diabetes/insulin resistance
 - Possible increased risk of MI
 - PR and QT prolongation
- **Ritonavir:**
 - GI intolerance
 - Hepatitis



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Adverse Effects: Integrase Inhibitor

- **Raltegravir**
 - Nausea
 - Headache
 - Diarrhea
 - CPK elevation



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Adverse Effects: CCR5 Antagonist

- **Maraviroc**
 - Drug-drug interactions
 - Rash
 - Abdominal pain
 - Upper respiratory tract infections
 - Cough
 - Hepatotoxicity
 - Musculoskeletal symptoms
 - Orthostatic hypotension



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Drug Interactions with ARVs

- Certain ARVs, particularly PIs and NNRTIs, have significant drug interactions with other ARVs and other medications
- Interactions may be complex and difficult to predict
- Coadministration of some ARVs with other ARV or non-ARV medications may require dosage adjustment, and some combinations may be contraindicated
- Check for interactions before prescribing
- Increases in serum drug levels caused by inhibitors of metabolism may increase risk of medication toxicity, whereas decreases in drug levels caused by inducers of metabolism may cause treatment failure
- Some drug interactions may be exploited, eg, low-dose RTV (a strong CYP3A4 inhibitor) may be used as a pharmacokinetic enhancer to increase concentrations and prolong the half-life of other PIs



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Drug Interactions with ARVs

- All PIs and NNRTIs are metabolized by the hepatic CYP 450 system, particularly the CYP3A4
- **Protease Inhibitors**
 - All PIs are CYP3A4 substrates, and their serum levels may be affected by CYP inducers or inhibitors
 - Some PIs also are inducers or inhibitors of other CYP isoenzymes or of P-glycoprotein (PGP) or other transporters
- **NNRTIs**
 - Substrates of CYP3A4, can act as inducer (NVP) or mixed inducer and inhibitor (EFV)
 - ETR is substrate of 3A4, 2C9, and 2C19; and inhibitor of 2C9 and 2C19



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Drug Interactions with ARVs

- **NRTIs**
 - No hepatic metabolism, but some NRTIs may interact via other mechanisms (eg, decrease in ATV concentration if coadministered with TDF, proton pump inhibitors, H2 receptor antagonists)
- **Integrase inhibitor**
 - RAL: eliminated by glucuronidation; inducers of UGT1A1 (eg, rifampin) can reduce RAL concentration
- **CCR5 antagonist**
 - MVC: substrate of CYP3A and PGP; concentrations are significantly affected by CYP3A inhibitors or inducers; dosage adjustment necessary



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Common Drug Interactions with ARVs: Require Dosage Modification or Cautious Use

- Lipid-lowering agents
- Antimycobacterials, especially rifampin*
- Antifungals
- Psychotropics – midazolam, triazolam
- Ergot alkaloids
- Antihistamines – astemizole
- Anticonvulsants
- Oral hormonal contraceptives, including emergency contraception (Plan B): may require alternative or second method
- Methadone
- Erectile dysfunction agents
- Herbs – St. John's wort

* Of NNRTIs and PIs, rifampin may be used only with full-dose RTV or with EFV.



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ARV-ARV Interactions: Require Dosage Modification or Cautious Use

- EFV, NVP, or ETR with PIs
- ATV + TDF
- ddl + TDF
- ddl + d4T
- MVC + many PIs
- MVC + EFV or ETR



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The HIV-Infected Adolescent

Transitioning care:

- Recognize differences between many adolescent and adult HIV care models
- Consider issues of independence, autonomy, decisional capacity, confidentiality, consent, medical insurance
- Recognize different biomedical and psychosocial needs of perinatally infected vs. behaviorally infected youth



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