AETC AIDS Education & Training Center Program
National Coordinating Resource Center

Management of the Treatment-Experienced Patient

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents

April 2015

AETC NRC Slide Set

About This Presentation

These slides were developed using the April 2015 guidelines and updated in July 2016. The intended audience is clinicians involved in the care of patients with HIV.

Because the field of HIV care is rapidly changing, users are cautioned that the information in this presentation may become out of date quickly.

It is intended that these slides be used as prepared, without changes in either content or attribution. Users are asked to honor this intent.

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The Treatment-Experienced Patient: Contents

- Considerations
- Evaluation and Management of Virologic Failure
- Poor CD4 Recovery and Persistent Inflammation Despite Viral Suppression
- Regimen Switching in Setting of Virologic Suppression
- Treatment Interruption Testing for Resistance

Treatment-Experienced Patients

- The recommended initial ARV regimens should suppress HIV to below the lower level of detection (LLOD) of HIV RNA assays
- Nonetheless, >20% of patients on ART are not virologically suppressed
  - Virologic rebound or failure of virologic suppression often results in resistance mutations
- In patients with suppressed viremia:
  - Assess adherence frequently
  - Simplify ARV regimen as much as possible
- Patients with ART failure: assess and address aggressively

Treatment-Experienced Patients

- Assessment and management of ART failure is complex: consult with experts

Definitions of Virologic Response

- Virologic suppression:
  - Confirmed HIV RNA below LLOD (eg, <50 copies/mL)
- Virologic failure:
  - Inability to achieve or maintain HIV RNA <200 copies/mL
- Incomplete virologic response:
  - Confirmed HIV RNA ≥200 copies/mL after 24 weeks on ART
- Virologic rebound:
  - Confirmed HIV RNA ≥200 copies/mL after virologic suppression
- Virologic blip:
  - An isolated detectable HIV RNA level that is followed by a return to virologic suppression

Virologic Failure

- Failure of current first-line regimens usually caused by suboptimal adherence or transmitted drug resistance

Virologic Failure (2)

- Causes of treatment failure include:
  - Patient factors
    - Higher pretreatment HIV RNA (depending on the ART regimen)
    - Lower pretreatment CD4 (depending on the ART regimen)
    - Comorbidities (eg, substance abuse, psychiatric or neurocognitive issues)
    - Drug resistance
    - Suboptimal adherence, missed clinic appointments
    - Interruptions in access to ART

Virologic Failure (3)

- Causes of treatment failure include (cont.):
  - ARV regimen factors
    - Toxicity and adverse effects
    - Pharmacokinetic problems
    - Suboptimal ARV potency
    - Prior exposure to nonsuppressive regimens
    - Food requirements
    - High pill burden and/or dosing frequency
    - Drug-drug interactions
    - Prescription errors
    - Cost and affordability of ARVs

Virologic Failure: Assessment

- Approach to subsequent ART depends on the cause of regimen failure and remaining ARV options
- Review medical history
  - HIV RNA, CD4 changes over time
  - HIV-related clinical events
  - ARV treatment history
  - Results of previous resistance tests
  - Adherence, tolerability, concomitant medications
- Physical examination for signs of clinical progression

Virologic Failure: Assessment (2)

- Explore in depth issues of:
  - Suboptimal adherence
    - Carefully assess adherence, identify and address underlying causes of incomplete adherence (eg, intolerance, cost or access issues, depression, substance abuse)
    - Simplify regimen, if possible
  - Medication intolerance
    - Assess ARV tolerance, severity and duration of side effects (even minor side effects can affect adherence
    - Consider symptomatic treatments, ARV switches

Virologic Failure: Assessment (3)

- Pharmacokinetic issues
  - Review food requirements for each ARV, history of vomiting or diarrhea that may cause malabsorption, possible adverse drug-drug interactions with concomitant medications or supplements; consider therapeutic drug monitoring if malabsorption or drug interactions suspected
- Suspected drug resistance
  - Drug resistance testing
  - Treatment history
  - Previous resistance test results
  - Drug resistance usually is cumulative – consider all treatment history and test results

Virologic Failure: Management

- If virologic failure persists, resistance testing should be done and ART should be changed as soon as possible
  - Ongoing viral replication promotes selection of drug resistance mutations
  - Virologic responses to new regimen likely to be better if HIV RNA is lower or CD4 count is higher
  - Avoid treatment interruption, which may cause rapid worsening of CD4, HIV RNA, and clinical status

Virologic Failure: Management (2)

- Goal of ART change: to establish virologic suppression (HIV RNA <LLOD)

General principles of selecting new ART:

- New regimen should contain at least 2 (preferably 3) fully active agents
  - Based on ARV history, resistance testing, and/or novel mechanism of action
- In general, 1 active drug should not be added to a failing regimen (drug resistance is likely to develop quickly)
- Consult with experts

Virologic Failure: Addressing Viremia

- Low-level viremia (LLOD to 1,000 copies/mL):
  - LLOD-<200 copies/mL
    - Transient “blips”: no change in ART required
    - Persistent RNA between LLOD and 200: no consensus but low risk of new resistance; monitor at least every 3 months
  - Persistent HIV RNA >200 to <1,000 copies/mL
    - Confirm RNA; assess causes as above
    - Resistance is likely to develop; do resistance test if possible, consider ART change according to results

Virologic Failure: Addressing Viremia (2)

- HIV RNA >1,000 copies/mL and no resistance identified:
  - Usually caused by suboptimal adherence: assess thoroughly; also drug-drug and drug-food interactions
  - May restart same regimen if no side effects or interactions; otherwise start new ART
    - Recheck HIV RNA in 2-4 weeks, do genotype of RNA >500 copies/mL

Virologic Failure: Addressing Viremia (3)

- HIV RNA >1,000 copies/mL and drug resistance:
  - Goal: suppress HIV RNA if possible
  - Change regimen early to prevent further resistance
    - Especially consider stopping NNRTI, RAL, and ENF in a failing regimen

Management of Virologic Failure: First ART Failure

- Failure of NNRTI + NRTIs
  - Often resistance to NNRTI +/– 3TC and FTC
  - Boosted PI + NRTIs or RAL often effective
- Failure of boosted PI + NNRTIs
  - Most have no resistance or resistance only to 3TC/FTC
  - Assess adherence and drug interactions; may continue same ART or change (eg, if tolerability issues)

Management of Virologic Failure: First ART Failure (2)

- Failure of INSTI + NRTIs
  - May have resistance to 3TC/FTC +/- INSTI resistance, (if failing RAL or EVG/c)
  - Consider boosted PI + NRTIs or an INSTI (if no INSTI resistance)
  - Consider regimen with boosted PI + DTG if testing predicts susceptibility to DTG

Management of Virologic Failure: Second-Line Failure and Beyond

- Drug resistance with treatment options that allow full virologic suppression
  - If fully active boosted PI is available:
    - Boosted PI + NRTIs or INSTI (if susceptible to INSTI)
  - If no fully active boosted PI:
    - Regimen should include at least 2 (preferably 3) fully active agents, if possible
    - Select ARVs that are likely to be active based on ART history, past and present resistance tests, tropism testing (if CCR5 antagonist is considered)

Management of Virologic Failure: Second-Line Failure and Beyond (2)

- Multidrug resistance without treatment options that allow full virologic suppression
  - Goals: preserve immunologic function, prevent clinical progression, minimize new resistance to drug classes in which new effective drugs may become available
  - No consensus: consult with experts
  - No reason to continue NNRTIs, EVG, RAL, T20 if resistance to them is present: not effective and risk of accumulating additional resistance mutations that may limit future ARV options
    - Even with partial virologic suppression, ART decreases risk of HIV progression

Management of Virologic Failure: Second-Line Failure and Beyond (3)

- Previous treatment and suspected drug resistance, in need of ART but with limited information about past ARV history
  - Obtain medical records and prior resistance test results, if possible
  - If ARV and resistance history is not available, consider restarting the most recent ARV regimen and assessing drug resistance in 2-4 weeks to guide choice of next regimen, or start 2-3 ARVs predicted to be active based on patient's history

Isolated CNS Virologic Failure and New Onset Neurologic Symptoms

- Rarely, patients may present with new (usually subacute) neurological signs and symptoms associated with CNS virologic failure
  - Breakthrough of HIV RNA in CNS compartment despite HIV RNA suppression in plasma
  - MRI of brain shows abnormalities; CSF may show lymphocytic pleocytosis and elevated HIV RNA (higher than in plasma), drug-resistant HIV virus in the CSF HIV
- Must distinguish from other CNS infections, mild asymptomatic CSF RNA elevation, neurocognitive impairment not associated with CNS viral breakthrough

Isolated CNS Virologic Failure and New Onset Neurologic Symptoms (2)

- Management:
  - Consider drug resistance testing of HIV in CSF, if available
  - Change ART based on resistance test results, treatment history
  - Consider CNS pharmacokinetics of ARVs

Poor CD4 Recovery and Persistent Inflammation Despite Viral Suppression

- Morbidity and mortality are higher in HIV-infected individuals than in the general population, even with viral suppression
  - eg, cardiovascular disease, many non-AIDS cancers and infections, COPD, osteoporosis, diabetes, liver disease, kidney disease, neurocognitive dysfunction
  - Likely related to poor CD4 recovery, persistent immune activation, and inflammation, as well as patient behaviors and ARV toxicity

Poor CD4 Recovery and Persistent Inflammation Despite Viral Suppression (2)

- Poor CD4 recovery
  - Persistently low CD4 (especially <200 cells/μL, but also up to at least 500 cells/μL) despite viral suppression on ART is associated with risk of illness and mortality
  - Higher risk of suboptimal response with lower pretreatment CD4 counts

Poor CD4 Recovery and Persistent Inflammation Despite Viral Suppression (3)

- Management:
  - Evaluate for underlying causes (eg, malignancy, infections)
  - If possible, discontinue concomitant medications that may decrease CD4 cells (eg, AZT, combination of TDF + ddI), interferon, prednisone)
  - No consensus on management of patients without evident causes
    - Changing or intensifying the ARV regimen has not been shown to be beneficial
    - Immune-based therapies: unproven benefit; should be used only in clinical trials

Poor CD4 Recovery and Persistent Inflammation Despite Viral Suppression (4)

- Persistent immune activation and inflammation
  - Systemic immune activation and inflammation may be independent mediators of risk of morbidity and mortality in patients with viral suppression on ART
    - Association with morbidity/mortality is largely independent of CD4 count
  - Immune activation and inflammation decrease with suppression of HIV through ART, but do not return to normal
  - Poor CD4 recovery on ART (eg, CD4 <350 cells/μL) associated with greater immune system activation and inflammation

Poor CD4 Recovery and Persistent Inflammation Despite Viral Suppression (5)

- Causes of persistent immune activation not completely clear: likely include HIV persistence, coinfections, microbial translocation
  - No proven interventions
    - ART intensification or modification: not consistently effective in studies
    - Antiinflammatory medications and others are being studied
    - Clinical monitoring with immune activation or inflammatory markers is not currently recommended
  - Focus on maintaining viral suppression with ART, reducing risk factors (eg, smoking, diet, exercise), managing comorbidities (eg, hypertension, hyperlipidemia, diabetes)

Regimen Switching in Setting of Virologic Suppression

- Changing a suppressive ARV regimen to:
  - Reduce pill burden and dosing frequency to improve adherence
  - Enhance tolerability, decrease toxicity
  - Change food or fluid requirements
  - Minimize or address drug interactions
  - Allow for optimal ART during pregnancy
  - Reduce costs

Regimen Switching in Setting of Virologic Suppression (2)

- Goals: improve patient's quality of life, maintain ART adherence, avoid long-term toxicities, reduce risk of virologic failure
  - Absent drug resistance, switching from a complex regimen, one with higher pill burden, dosing frequency, or more toxic ARVs:
    - Generally improves or does not worsen adherence, maintains viral suppression, and may improve quality of life
- Consider known or suspected drug resistance in making decisions

Regimen Switching in Setting of Virologic Suppression (3)

Principles

- Maintain viral suppression and avoid jeopardizing future ARV options
- Review full ARV history, including all resistance test results and adverse effects
  - Previously acquired resistance mutations generally are archived and may reappear under selective drug pressure
  - Resistance often may be inferred from patient's treatment history
    - eg, resistance to 3TC and FTC should be assumed if virologic failure occurred in a patient taking one of these NRTIs, even if the mutation is not seen in resistance test results
  - Consult with an HIV specialist if history of resistance

Regimen Switching in Setting of Virologic Suppression (4)

- Within-class switches:
  - Usually maintain viral suppression if no resistance to other ARVs in the same drug class
  - eg, from EFV to RPV, TDF to TAF, RAL to DTG
- Between-class switches:
  - Usually maintains viral suppression if there is no resistance to the components of the regimen
  - Avoid this type of switch if there is doubt about the activity of any agents in the regimen
  - eg, from boosted PI or NNRTI to INSTI
- RTV-boosted PI + 3TC or FTC:
  - Growing evidence that boosted PI + 3TC can maintain viral suppression in ART-naive patients with no baseline resistance and those with sustained viral suppression
  - May be reasonable if use of TDF, TAF, or ABC is contraindicated

Regimen Switching in Setting of Virologic Suppression (5)

Switch strategies not recommended:

- RTV-boosted PI monotherapy
  - Less likely to maintain viral suppression
- Switching to maraviroc
  - Insufficient data on use of proviral DNA to determine tropism in virologically suppressed patients
- Other types of switches are under investigation

- Closely monitor tolerability, viral suppression, adherence, and toxicity in first 3 months after regimen switch

Interruption of ART

- May cause viral rebound, immune decompensation, and clinical progression
- Not recommended as a treatment strategy; increases risk of HIV- and non-HIV-related complications
- Potential risks and benefits vary according to patient's clinical and immunologic status, duration of interruption, and other factors
- Short-term treatment interruptions may be necessary (eg, drug toxicity, inability to take oral medications, nonavailability of drugs)

Interruption of ART: Short-Term

Considerations for stopping ART

- In case of severe or life-threatening toxicity:
  - Stop all drugs simultaneously
- Planned short-term interruption
  - When all ARVs have similar half-lives:
    - Stop all drugs simultaneously
  - When ARVs have different half-lives:
    - Stopping all ARVs simultaneously may result in functional monotherapy
    - Consider staggered discontinuation, or substitution of shorter half-life ARVs (see below)

Interruption of ART: Long-Term

Potential risks, including:

- Viral rebound
- CD4 decline
- Acute retroviral syndrome
- Disease progression, death
- Development of drug resistance
- Increase in risk of HIV transmission

Treatment discontinuation is not recommended outside clinical trials

Interruption of ART: ARV-Specific Issues

Discontinuation of EFV, ETR, or NVP:

- These ARVs have long half-lives; stopping drugs in an ART regimen simultaneously may result in functional monotherapy or dual therapy
- The optimal interval between stopping these and other ARVs is not known
- Consider substitution of a boosted PI for the NNRTI for a period of time before stopping all ARVs

Interruption of ART: ARV-Specific Issues (2)

Discontinuation and reintroduction of NVP:

- If NVP has been interrupted for more than 2 weeks, it should be restarted with the usual dosage-escalation period

Interruption of ART: ARV-Specific Issues (3)

Discontinuation of FTC, 3TC, TAF, or TDF in patients with hepatitis B (HBV):

- Flare of hepatitis may occur on discontinuation of any of these ARVs
- Monitor closely
- Consider initiating entecavir for HBV treatment
  - Use only in patients not on suppressive ART

Interruption of ART: Patient Counseling

If therapy must be discontinued, counsel patients on:

- Need for close clinical and laboratory monitoring
- Risks of treatment interruption
- Behavioral guidelines to reduce risk of HIV transmission

Testing for Drug Resistance

- Recommended in case of virologic failure, to determine role of resistance and maximize the number of active drugs in a new regimen
- Combine with obtaining a drug history and maximizing drug adherence
- Perform while patient is taking ART (or within 4 weeks of regimen discontinuation)
  - May consider resistance testing >4 weeks after treatment interruption, recognizing that resistance mutations may be present but undetected

Testing for Drug Resistance (2)

- HIV RNA generally must be >1,000 copies/mL (may be successful if >500 copies/mL)
- A new genotype assay analyzes proviral DNA in persons with HIV RNA below limit of detection; clinical utility is not known

Genotyping

- Detects drug resistance mutations in specific genes (eg, reverse transcriptase, protease, integrase)
  - Order specific genotype for integrase inhibitor resistance, if suspected (some standard genotype tests only RT and PR genes)
- Sequencing or probing
- Results within 1-2 weeks
- Interpretation of mutations and cross-resistance is complex
- Consultation with specialists is recommended

Phenotyping

- Measures the ability of viruses to grow in various concentrations of ARV drugs
- Results within 2-3 weeks
- More expensive than genotyping
- The ratio of the IC50s of the test and reference viruses is reported as the fold increase in IC50, or fold resistance
- Interpretation may be complex
- Consultation with specialists is recommended

Drug Resistance Testing: Limitations

- Lack of uniform quality assurance
- Relatively high cost
- Insensitivity for minor viral species (<10-20%)
- Standard resistance tests require HIV RNA >500-1,000 copies/mL
  - Proviral DNA assay – no clinical data

Coreceptor Tropism Assay

- Test for tropism before using CCR5 antagonist
  - MVC should be given only to patients with exclusive CCR5 tropism
  - Current commercially available tropism assay is 100% sensitive for CXCR5 clones that make up ≥0.3% of the population
- Standard phenotypic assay requires plasma HIV RNA ≥1,000 copies/mL
  - Proviral DNA assay can be used if HIV RNA is below limit of detection (not clinically validated)
- Consider in patients with virologic failure on a CCR5 antagonist (does not rule out resistance)

Websites to Access the Guidelines

- http://www.aidsetc.org
- http://aidsinfo.nih.gov

About This Slide Set

- This presentation was updated by Susa Coffey, MD, for the AETC National Coordinating Resource Center in July 2016.
- See the AETC National Coordinating Resource Center website for the most current version of this presentation:

http://www.aidsetc.org