ACTHIV 2017: A State-of-the-Science Conference for Frontline Health Professionals
What ART to Start in a Patient Newly Diagnosed with HIV

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Learning Objectives

■ Describe the factors in selecting antiretroviral therapy for newly diagnosed persons with HIV infection

■ Select the best choices for initial treatment of the newly-diagnosed HIV infected patient
When was the first DHHS Guideline on use of Antiretrovirals released?

1. 1989
2. 1993
3. 1996
4. 1998
5. 2001
First Antiretroviral Drug Guidelines - 1993

Special Communication

Antiretroviral Therapy for Adult HIV-Infected Patients

Recommendations From a State-of-the-Art Conference

Merle A. Sande, MD; Charles C. J. Carpenter, MD; C. Glenn C. Jay P. Sanford, MD; for the National Institute of Allergy and Infectious Diseases State-of-the-Art Panel on Anti-Retroviral Therapy for Adult HIV-

JAMA Dec 1, 1993
First ART Guidelines -

• When to Start,
• What to Start with,
• When to Switch

Antiretroviral Therapy for HIV-Infected Adults: Recommendations From 1993 NIAID State-of-the-Art Conference

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>CD4+ Range, Cell Count x 10^9/L</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Previous Antiretroviral Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt;0.50</td>
<td>No therapy</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.20-0.50</td>
<td>Zidovudine or no therapy</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>0.20-0.50</td>
<td>Zidovudine</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&lt;0.20</td>
<td>Zidovudine</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>&lt;0.20</td>
<td>Zidovudine</td>
</tr>
</tbody>
</table>

| Previous Antiretroviral Therapy |
|---------------------------------|---------------------------------|
| Stable                          | ≥0.30                           | Continue zidovudine |
| Stable                          | <0.30                           | Continue zidovudine or change to didanosine |
| Progressing                     | 0.05-0.50                       | Change to didanosine or zalcitabine |
| Progressing                     | <0.05                           | Change to didanosine or zalcitabine |

Intolerant to Zidovudine

| Stable or progressing            | <0.50                           | Change to didanosine or zalcitabine |

*HIV indicates human immunodeficiency virus; and NIAID, National Institute of Allergy and Infectious Diseases. Refer to text for supporting data and illustrative clinical scenarios.
Report of the NIH Panel to Define
Principles of Therapy of HIV Infection

and

Guidelines for the Use of Antiretroviral
Agents in HIV-Infected Adults
and Adolescents
TABLE 6. Recommended antiretroviral agents for treatment of established HIV infection

**Preferred:** Strong evidence of clinical benefit and/or sustained suppression of plasma viral load

(2, 34, 35)

One choice each from column A and column B. Drugs are listed in random, not priority, order:

<table>
<thead>
<tr>
<th>Column A</th>
<th>Column B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir (AI)</td>
<td>ZDV + ddI (AI)</td>
</tr>
<tr>
<td>Nelfinavir (AI)</td>
<td>d4T + ddI (AI)</td>
</tr>
<tr>
<td>Ritonavir (AI)</td>
<td>ZDV + ddC (AI)</td>
</tr>
<tr>
<td>Saquinavir-SGC* (AI)</td>
<td>ZDV + 3TC(^{#}) (AI)</td>
</tr>
<tr>
<td>Ritonavir + Saquinavir-SGC or HGC(^{\dagger}) (BII)</td>
<td>d4T + 3TC(^{#}) (AI)</td>
</tr>
</tbody>
</table>

**Alternative:** Less likely to provide sustained virus suppression; (36–38)

1. NNRTI (Nevirapine)\(^{\dagger}\) + 2 NRTIs (Column B, above) (BII)
2. Saquinavir-HGC + 2 NRTIs (Column B, above) (BII)

**Not generally recommended:** Strong evidence of clinical benefit, but initial virus suppression is not sustained in most patients (39, 40)

1. NRTIs (Column B, above) (CI)

**Not recommended**: Evidence against use, virologically undesirable, or overlapping toxicities

All monotherapies (DI)

d4T + ZDV (DI)

ddC + ddI\(^{\dagger\dagger}\) (DII)

ddC + d4T\(^{\dagger\dagger}\) (DII)

ddC + 3TC\(^{\dagger\dagger}\) (DII)
Approach to the Patient with HIV:

4 Steps

**Step 1:** History, Examination and Lab Tests

**Step 2:** Opportunistic infection prophylaxis (if indicated)

**Step 3:** Antiretroviral therapy and monitoring

**Step 4:** Preventive care, including vaccine
Rating Scheme for Recommendations

- **Strength of recommendation:**
  - A: Strong
  - B: Moderate
  - C: Optional

- **Quality of evidence:**
  - I: $\geq 1$ randomized controlled trials
  - II: $\geq 1$ well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; also randomized switch studies and bioavailability/bioequivalence studies
  - III: Expert opinion
Current ARV Medications

**NRTI**
- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir DF (TDF)
- Tenofovir alafenamide (TAF)*
- Zidovudine (AZT, ZDV)

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

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

**Integrase Inhibitor (INSTI)**
- Dolutegravir (DTG)
- Elvitegravir (EVG)
- Raltegravir (RAL)

**Fusion Inhibitor**
- Enfuvirtide (ENF, T-20)

**CCR5 Antagonist**
- Maraviroc (MVC)

**Pharmacokinetic (PK) Booster**
- Ritonavir (RTV)
- Cobicistat (COBI)

* TAF available only in coformulations: TAF/FTC, RPV/TAF/FTC, EVG/COBI/TAF/FTC
Initial ART Regimens: DHHS Categories

- **Recommended**
  - Easy to use
  - Durable virologic efficacy
  - Favorable tolerability and toxicity profiles

- **Alternative**
  - Effective but have potential disadvantages, limitations in certain patient populations, or less supporting data
  - May be the optimal regimen for individual patients

- **Other**
  - Reduced virologic activity; limited supporting data; or greater toxicities, higher pill burden, more drug interactions, or other limiting factors
# Initial Regimens: Recommended

<table>
<thead>
<tr>
<th>INSTI based</th>
<th>DTG/ABC/3TC; only if HLA-B*5701 negative (AI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG (QD) + FTC + TDF (AI) or TAF (AII)</td>
</tr>
<tr>
<td></td>
<td>EVG/COBI/TDF/FTC; only if pre-ART CrCl &gt;70 mL/min (AI)</td>
</tr>
<tr>
<td></td>
<td>EVG/COBI/TAF/FTC (AI)</td>
</tr>
<tr>
<td></td>
<td>RAL + FTC + TDF (AI) or TAF (AII)</td>
</tr>
<tr>
<td>PI based</td>
<td>DRV/r (QD) + FTC + TDF (AI) or TAF (AII)</td>
</tr>
</tbody>
</table>

Note:
3TC can be used in place of FTC and vice versa; TDF: caution if renal insufficiency

IASUSA 2016 recommends INSTI only with either TAF/FTC or ABC/3TC

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## Initial Regimens: Alternative

| NNRTI based | ▪ EFV/TDF/FTC (BⅠ)  
| ▪ EFV plus TAF/FTC (BⅡ)  
| ▪ RPV/TDF/FTC (BⅠ) or RPV/TAF/FTC (BⅡ)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm³ |

| PI based | ▪ ATV/c or ATV/r plus either TDF/FTC (BⅠ) or TAF/FTC (BⅡ)  
| ▪ DRV/c (BⅢ) or DRV/r (BⅡ) plus ABC/3TC—if HLA-B*5701 negative  
| ▪ DRV/c plus either TDF/FTC (BⅡ) or TAF/FTC (BⅡ) |

**Note:**  
3TC can be used in place of FTC and vice versa; TDF: caution if renal insufficiency

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| If HIV RNA <100,000 copies/mL and HLA-B*5701 negative: | (ATV/c (CIII) or ATV/r (CII) ) + ABC/3TC  
| | EFV + ABC/3TC (Cl)  
| | RAL + ABC/3TC (CII) |  
| Others to consider when TAF, TDF, or ABC cannot be used | DRV/r + RAL (BID) (Cl) – only if HIV RNA <100,000 copies/mL and CD4 >200 cells/µL  
| | LPV/r + 3TC (Cl) |  

Note: 3TC can be used in place of FTC and vice versa

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## Individualized Regimen Selection

<table>
<thead>
<tr>
<th>Pre-ARV Characteristics</th>
<th>ART-Regimen Characteristics</th>
<th>Concomitant Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>- CD4</td>
<td>- Virologic potency</td>
<td>- Chronic kidney disease</td>
</tr>
<tr>
<td>- HIV RNA</td>
<td>- Adverse effect profile</td>
<td>- CV disease, hyperlipidemia</td>
</tr>
<tr>
<td>- HLA-B*5701 status</td>
<td>- Pill burden</td>
<td>- Psychiatric illnesses</td>
</tr>
<tr>
<td>- Pregnancy status</td>
<td>- Co-formulation</td>
<td>- Osteoporosis</td>
</tr>
<tr>
<td>- Resistance testing results</td>
<td>- Dosing frequency</td>
<td>- Co-infection (e.g. HBV, HCV, TB)</td>
</tr>
<tr>
<td>- Must treat before resistance testing results</td>
<td>- Drug Interaction potential</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- (Cost)</td>
<td></td>
</tr>
</tbody>
</table>
Which ARV Drug(s) Will You **Not** Use

- Recent hospitalization for depression
- With chronic renal insufficiency and uncontrolled diabetes
- HLA-B*5701
- HIV RNA 250,000 copies/mL
- With active TB receiving rifampin
- CD4 count 55 cells/mm³
25 yo wants STR, CD4 147 and VL 180K. HLA B5701 positive. You suggest:

1. RPV/TAF/FTC
2. RPV/ TDF/FTC
3. EVGc /TAF/FTC
4. DTG plus TDF/FTC
5. DTG/ABC/3TC
### Selecting Initial ART Regimen: Selected Clinical Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **CD4 <200**                     | Do not use: higher rate of virologic failure  
  - RPV-based ART  
  - DRV/r + RAL |
| **HIV RNA >100,000**             | Do not use: higher rate of virologic failure  
  - RPV-based ART  
  - ABC/3TC + EFV or ATV/r  
  - DRV/r + RAL |
| **HLA-B*5701 positive**          | Do not use ABC: risk of abacavir hypersensitivity                                  |
| **Must treat before resistance test results are known** | Avoid NNRTI-based regimens: transmitted resistance more likely than with PI or INSTI  
  Recommended:  
  - DRV/r + TAF/FTC or TDF/FTC  
  - DTG + TAF/FTC or TDF/FTC |

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# Single Tablet Regimens (STR)

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>ARV Drugs</th>
<th>Image (Pill size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla</td>
<td>Efavirenz 600mg + TDF 300mg + emtricitabine 200mg</td>
<td><img src="image1.png" alt="Atripla Image" /></td>
</tr>
<tr>
<td>Complera</td>
<td>Rilpivirine 25mg + TDF 300mg + emtricitabine 200mg</td>
<td><img src="image2.png" alt="Complera Image" /></td>
</tr>
<tr>
<td>Odefsey</td>
<td>Rilpivirine 25mg + TAF 25mg + emtricitabine 200mg</td>
<td><img src="image3.png" alt="Odefsey Image" /></td>
</tr>
<tr>
<td>Stribild</td>
<td>Elvitegravir 150mg + cobicistat 150mg + TDF 300mg + emtricitabine 200mg</td>
<td><img src="image4.png" alt="Stribild Image" /></td>
</tr>
<tr>
<td>Genvoya</td>
<td>Elvitegravir 150mg + cobicistat 150mg + TAF 10mg + emtricitabine 200mg</td>
<td><img src="image5.png" alt="Genvoya Image" /></td>
</tr>
<tr>
<td>Triumeq</td>
<td>Dolutegravir 50mg + abacavir 600mg + lamivudine 300mg</td>
<td><img src="image6.png" alt="Triumeq Image" /></td>
</tr>
</tbody>
</table>
# Selecting Initial ART Regimen: Selected Clinical Scenarios

<table>
<thead>
<tr>
<th>One-pill regimen</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG/ABC/3TC (only if HLA-B*5701 negative)</td>
<td>EFV/TDF/FTC</td>
</tr>
<tr>
<td>EFV/TDF/FTC</td>
<td>EVG/COBI/TAF/FTC</td>
</tr>
<tr>
<td>EVG/COBI/TDF/FTC</td>
<td>EVG/COBI/TDF/FTC</td>
</tr>
<tr>
<td>RPV/TAF/FTC (if HIV RNA &lt;100,000 copies/mL and CD4 &gt;200 cells/µL)</td>
<td>RPV/TDF/FTC (if HIV RNA &lt;100,000 copies/mL and CD4 &gt;200 cells/µL)</td>
</tr>
<tr>
<td>Should be taken with food:</td>
<td>Should be taken on empty stomach: EFV</td>
</tr>
<tr>
<td>ATV/r or ATV/c</td>
<td>EVG/c/TAF/FTC</td>
</tr>
<tr>
<td>DRV/r or DRV/c</td>
<td>EVG/c/TDF/FTC</td>
</tr>
<tr>
<td>EVG/c/TAF/FTC</td>
<td>RPV/TAF/FTC</td>
</tr>
<tr>
<td>EVG/c/TDF/FTC</td>
<td>RPV/TDF/FTC</td>
</tr>
</tbody>
</table>

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### Selecting Initial ART Regimen: Selected Clinical Scenarios

| Chronic kidney disease (eGFR <60 mL/min) | Avoid TDF; use ABC or TAF  
|                                          |   - ABC not associated with renal dysfunction  
|                                          |   - TAF has less impact on renal function and proteinuria than TDF; may be used if eGFR >30 mL/min  
|                                          | Options when ABC or TAF cannot be used:  
|                                          |   - LPV/r + 3TC  
|                                          |   - DRV/r + RAL (if HIV RNA <100,000 copies/mL and CD4 >200 cells/µL)  
| Liver disease with cirrhosis             | Some ARVs contraindicated or require dosage modification  
|                                          | Evaluation by expert in advanced liver disease is recommended |

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## Selecting Initial ART Regimen:
### Selected Clinical Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **Osteoporosis**       | - Avoid TDF: associated with greater decrease in BMD, osteomalacia, urine phosphate wasting  
                         | - Use ABC or TAF                                                                |
|                        |   - Associated with smaller decreases in BMD                                    |
|                        |   - ABC may be used if HLA-B*5701 negative (if HIV RNA >100,000 copies/mL, do not use with EFV or ATV/r) |
| **Psychiatric illness**| - Consider avoiding EFV and RPV: can exacerbate psychiatric symptoms; may be associated with suicidality |
| **HIV-associated dementia** | - Avoid EFV  
                        | - Favor DRV- or DTG-based regimens (theoretical CNS penetration advantage, ? DTG AE) |

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## Selecting Initial ART Regimen: Selected Clinical Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High cardiac risk</strong></td>
<td>Consider avoiding ABC and LPV/r: increased CV risk in some studies</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>Adverse effects on lipids:</td>
</tr>
<tr>
<td></td>
<td>- PI/r or PI/c</td>
</tr>
<tr>
<td></td>
<td>- EFV</td>
</tr>
<tr>
<td></td>
<td>- EVG/c</td>
</tr>
<tr>
<td></td>
<td>Beneficial lipid effects:</td>
</tr>
<tr>
<td></td>
<td>- TDF</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>See Perinatal Guidelines</td>
</tr>
</tbody>
</table>
# Selecting Initial ART Regimen: Selected Clinical Scenarios

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **HBV**   | ▪ Use TDF or TAF with FTC or 3TC, whenever possible: use 2 NRTIs with activity against both HIV and HBV  
▪ If TDF and TAF are contraindicated: treat HBV with FTC or 3TC + entecavir + suppressive ART regimen |
| **HCV**   | ▪ Consult current recommendations |
| **TB**    | ▪ TAF not recommended with rifamycins  
▪ If rifampin is used:  
  ▪ EFV: no dosage adjustment needed  
  ▪ RAL: increase RAL to 800 mg BID  
  ▪ DTG: 50 mg BID (only if no significant INSTI mutations)  
▪ If PI-based regimen: use rifabutin in place of rifampin |

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## DTG associated with CNS AEs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Discontinuation due to any adverse event (12-month rate)</th>
<th>Discontinuation due to neuropsychiatric event (12-month rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>7.6%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>7.6%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>3.3%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

*de Boer M et al, AIDS 2016 Nov 28;30(18):2831-2834
Hoffman C, HIV Medicine 2017 Jan;18(1):56-63*
Cardiovascular Disease

- DAD data suggested Darunavir associated with increased CVD events
- Atazanavir cardio protective ? : Hyperbilirubinemia may protect against cardiovascular disease (CVD) by reducing oxidative stress and via its anti-atherogenic properties
Out of the box

- 35 year old man dx HIV, GT reveals K103N, M184V and K65R, HLA B5701 negative, all other labs normal. CD4 560 and HIV VL 77,000. You advise:

1. DTG/ABC/3TC
2. DTG/TDF/FTC
3. DTG/RPV
4. DRVr/RAL
5. EVGc/TAF/FTC
6. DTG monotherapy
Study Design: SWORD 1&2

- **Background**: Identical randomized, multinational, open-label, industry-sponsored, parallel-group, non-inferiority studies

- **Inclusion Criteria**:
  - On stable 3-drug ART (2 NRTI’s + INSTI, NNRTI, or boosted PI) for >6 months
  - 1\textsuperscript{st} or 2\textsuperscript{nd} regimen with no prior change due to virological failure
  - HIV RNA <50 for > 12 months
  - No HBV co-infection

Early switch phase

<table>
<thead>
<tr>
<th>DTG + RPV (n = 513)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue 3-Drug ART (n = 511)</td>
</tr>
<tr>
<td>48 weeks</td>
</tr>
</tbody>
</table>

Late switch phase

<table>
<thead>
<tr>
<th>DTG + RPV (n = 513)</th>
</tr>
</thead>
</table>

Primary endpoint: week 48 HIV RNA <50 copies/mL by snapshot analysis

Results
48-Week Virologic Response by Intention-to-Treat

- **DTG + RPV**: 95.0%
- **3-Drug ART**: 95.0%

*DTG + RPV met criteria for non-inferiority

*2 virologic failures in each arm; 1 in DTG + RPV arm had K101K/E

Monitoring after Starting ART

- Chemistries, BUN/Cr, LFTs: wk 2-8 after starting ART, then every 3-6 mo
- CBC/diff: every 3-6 mo.
- Fasting glucose or HbA1c: every 3-6 mo. If previously abnormal; every 12 mo. If normal
- Lipids: if abnormal, every 6 mo; normal: every 12 mo.
- U/A annually; every 6 mo. if receiving TDF or TAF

Monitoring after Starting ART

HIV RNA

- 2-4 wks after starting ART; then every 4-8 wks until undetectable
- First 2 yrs of ART: every 3-4 mo.
- After 2 yrs of virologic suppression, can extend to every 6 mo

CD4 count:

- 3 mo. after initiating ART
- First 2 yrs of ART: every 3-6 mo
- After 2 yrs of virologic suppression, CD4 300-500: every 12 mo.; CD4 >500, optional

67 yo MSM with newly diagnosed HIV

- Past medical history
  - Gastroesophageal reflux disease (GERD)
  - Allergic rhinitis
  - Hyperlipidemia (on simvastatin)
  - Diabetes on metformin

- Medications: omeprazole, fluticasone

- Smokes 1 ppd

- Creat clearance 57min/mL
- CD4 count 181 (13%), HIV RNA 178,000
- HIV genotype: no resistance mutations
- HLA-B5701 positive
Goals of Treatment

- Reduce HIV-related morbidity; prolong duration and quality of survival
- Restore and/or preserve immunologic function
- Maximally and durably suppress HIV viral load
- Prevent HIV transmission
Remember ALL

- SMX/TMP initiated for PCP prophylaxis
- Initiated TAF/FTC/elvitegravir/cobicistat
- Fluticasone changed to beclomethasone
- Vaccines: influenza; PCV-13 followed by PPSV-23 (>8 wks later); HAV and HBV; Meningococcal
- Hyperlipidemia: lifestyle changes; change to atorvastatin or rosuvastatin low dose or pitavastatin
- Focusing on smoking cessation and wt. loss counseling
- AAA screen, DEXA, Colonoscopy

Personal Opinion based on interpretation of literature and guidelines
All of the following should be considered when selecting ART except:

1. Hepatitis B coinfection
2. Genetics
3. Family history of allergy to sulfa medication
4. Baseline HIV viral load
5. Willingness to take medications
HIV Still Generates Rejection