Learning Objectives

After attending this presentation, participants will be able to:

- List the reasons for initiating antiretroviral therapy in all patients regardless of CD4 cell count
- Describe the potential advantages of newer approved antiretroviral therapy
- Describe the emergence of drug resistant variants on antiretroviral therapy in a developed-world setting
**Goals of Antiretroviral Therapy**

- Maintain or restore the health of people living with HIV-1 (PLWHIV) through suppression of HIV-1 replication
- Minimize or eliminate short and long-term adverse effects of the therapy
- Have therapies that are accessible to all PLWHIV
- Prevent transmission of HIV-1 to others via any route of exposure

**WHO/UNAIDS Goals**

- But an estimated 32 million infected

**START BY GETTING ALL HIV-INFECTED PATIENTS WHO ARE IN CARE ON ANTIRETROVIRAL THERAPY**
START: Serious AIDS Events

- 72% reduced risk of serious AIDS events with immediate ART
- 57% reduced risk of serious events or death with immediate ART
- 68% of primary endpoints occurred in patients with CD4+ cell counts > 500 cells/mm³

START: Reduced Risk of Cancers With Immediate ART

<table>
<thead>
<tr>
<th>Cancer Event</th>
<th>Immediate ART</th>
<th>Deferred ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi's sarcoma</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Lymphoma, NHL + HL</td>
<td>3</td>
<td>10</td>
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<tr>
<td>Prostate cancer</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Lung cancer</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Anal cancer</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Cervical or testis cancer</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Other types*</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>39</td>
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</tbody>
</table>

TEMPRANO: Immediate vs Deferred ART Initiation and IPT Delivery for African Pts


Cumulative Probability of Developing HIV-Related Illness (%) by Group

Mos From Randomization

Deferred ART
Deferred ART + IPT
Immediate ART
Immediate ART + IPT

Cumulative Probability of Death or Severe HIV-Related Illness (%)

Cumulative Probability of Death or Severe HIV-Related Illness (%)

HPTN 052: Reduced Risk of Partner Infection

• ART offered to all index pts in delayed ART arm from May 2011 after interim results
  – 84% of pts in delayed ART arm had initiated ART at Yr 1 and 98% prior to study closure
• 8 linked HIV infections diagnosed after seropositive patient started ART
  – All occurred before or soon after initiation or after virologic failure
• No linked HIV transmissions observed when index participant stably suppressed on ART

Cohen MS, et al. IAS 2015. Abstract MOAC0101LB.

Current HIV cascade estimates for 2014

Current HIV cascade estimates for 2014

**WHY IS ART (IF STARTED) SO SUCCESSFUL?**

Potent, relatively simple (multiple single tablets regimens)
Favorable PK
Well tolerated

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**Shift To Integrase Inhibitor-based Therapy**

1,773 patients initiating ART between 1996 and 2014 in the UCHCC, follow-up through 2015
UCHCC: UNC CFAR HIV Clinical Cohort

Persistence of Initial ART

- 1,773 patients initiating ART between 1996 and 2014 in the UCHCC, follow-up through 2015
- Persistence defined as no switch in anchor agent class

In CNICS cohort integrase inhibitor use was strongly associated with HIV RNA suppression in multivariate analysis see poster 1034 Simoni et al

There Remains a Substantial Treatment Gap

- TREATMENT GAP - Not all PLWHIV in care are treated or on fully suppressive therapy
  - Stigma, substance use, mental health, access to clinics, transportation, clinic capacity
  - Intolerant of current therapies, adherence (see above)
  - The need to treat an individual for up to 8 decades!
  - Renal, cardiovascular, liver and bone toxicity
  - Safety of ART in pregnancy
  - Therapy options for infants and children
  - Adherence, life chaos, treatment fatigue, tolerability
  - Aging and drug interactions (e.g. CYP 3A4 inhibition)
  - HIV-1 resistance to antiretrovirals will emerge
  - Especially in regions with limited viral load monitoring

Continued Improvement in Currently Available ART Classes

- Dolutegravir
  - Once daily, unboosted
  - Limited drug interactions, high barrier to resistance

- Tenofovir alafenamide fumarate
  - Equal efficacy with TDF containing therapies, less bone toxicity and renal tubular effects
  - Smaller mg dosing (25 mg)
  - Use in renal dysfunction (CrCl down to 30 cc/min)
  - Activity against NNRTI resistant variants (?)

- Two drug therapy
  - Less expensive, fewer toxicities?
A Randomized, Double-Blind Comparison of Tenofovir Alafenamide vs Tenofovir Disoproxil Fumarate, Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, for Initial HIV-1 Treatment: Week 96 Results

![Virologic Outcome](slide20.png)

- By 96 weeks, resistance developed in 10/866 (1.2%) on TAF vs 8/867 (0.9%) on TDF
  - M184V/I: 9 TAF, 6 TDF
  - K65R/N: 2 TAF, 3 TDF
  - Primary INSTI-R: 8 TAF, 5 TDF, all genotypically susceptible to DTG

![Treatment Difference (95% CI)](slide21.png)

- Treatment difference of 4.7% (95% CI 1.3, 7.9) favoring E/C/F/TAF

![Changes in Proteinuria Through Week 96](slide22.png)

- There were no cases of proximal tubulopathy in the E/C/F/TAF arm compared with 2 cases in E/C/F/TDF, including 1 that led to discontinuation

![Treatment Difference in Change in Spine and Hip BMD Through Week 96 by Age](slide23.png)

- After 2 years, TAF combined with E/C/F maintained high rates of virologic suppression (87%) and remained noninferior to TDF and continued to have a superior renal and bone safety profile

Wohl et al JAIDS 2016
**ART to Decrease Long-term Toxicity**

Switch from Tenofovir DF to Tenofovir alafenamide–containing therapy in patients with suppressed plasma HIV RNA levels.

Improvements in proximal renal tubular function


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**Study 112: Week 96 Changes After Switch to E/C/F/TAF in Patients With Renal Impairment**

- Median eGFR change after E/C/F/TAF switch
  - CDK-EPI Cr: 1.0 mL/min (n=158)
  - CDK-EPI CysC: 3.9 mL/min (n=157)
- Significant improvements after E/C/F/TAF switch (P<0.05)
  - Proteinuria
  - Renal tubular function
  - Spine and hip bone mineral density
- Maintained HIV RNA <50 copies/mL: 88%
- Virologic failure: 2% (5/242)
- No virologic data: 10% (23/242)

These 96-week data support the renal and bone safety of E/C/F/TAF in HIV patients with renal impairment (eGFR 30–69 mL/min).

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**GARDEL: Dual ART Noninferior to Triple ART in Tx-Naive Pts at Wks 48 and 96**

- Phase III, international, open-label, randomized study
- Safety and tolerability also similar between treatment arms

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Two drug ART to Achieve and Maintain Suppression
Dolutegravir plus 3TC 24 week data PADDLE Study

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<th>Week</th>
<th>pVL 1</th>
<th>pVL 2</th>
<th>pVL 3</th>
<th>pVL 4</th>
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<th>pVL 6</th>
<th>pVL 7</th>
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</table>

From week 8 onwards all patients had pVL < 50 copies/mL.
Figueroa et al (Pedro Cahn) 15th European AIDS Conference 2015

Two Drug ART Maintains Suppression
Latte: Cabotegravir (InSTI) + rilpivirine maintenance vs. EFV-based therapy

RESISTANT HIV-1 WILL ALWAYS BE WITH US

Four to eight decades of therapy!
Previous exposure to suboptimal treatment in the developed world
Limited monitoring of virologic response world-wide
Transmitted drug resistance
Virologic failure and resistance emergence on current first-line regimens is RARE

- 8,746 patients in UK CHIC study who initiated tenofovir-based first-line ART between 1998 and 2012
- Virological failure defined as 2 consecutive viral loads >200 copies/ml
- Considered major IAS-USA mutations from resistance tests at time of initial failure (30 days before, 90 days after)
- Multiple imputation used to account for missing resistance tests (56%)
- Analysis ignores treatment switches/interruptions

![Chart](chart.png)

Very Low Rates of Treatment-emergent Resistance with Boosted PI Regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>PI</th>
<th>Wk</th>
<th>Genotypes</th>
<th>Major PI Mutations</th>
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<tr>
<td>CASTLE</td>
<td>440</td>
<td>ATV/RTV</td>
<td>96</td>
<td>26</td>
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<tr>
<td>ACTG 1020H</td>
<td>463</td>
<td>ATV/RTV</td>
<td>96</td>
<td>83</td>
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<td>ATV/RTV</td>
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<td>NR</td>
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<tr>
<td>ARTEMIS</td>
<td>346</td>
<td>LPV/RTV</td>
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<td>46</td>
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<tr>
<td>FLAMINGO</td>
<td>242</td>
<td>DRV/RTV</td>
<td>48</td>
<td>NR</td>
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<tr>
<td>ACTG 103H</td>
<td>601</td>
<td>ATV/RTV</td>
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<td>75</td>
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</tbody>
</table>

**Single Tablet Regimen:**
- Among 4453 pts in these trials, only 2 pts developed major PI mutations at initial VF


Low Virologic Failure and Lack of Treatment-Emergent Resistance With Dolutegravir

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Follow-Up Wks</th>
<th>Treatment Arm</th>
<th>Virologic Failure, %</th>
<th>Dolutegravir-Related Primary Mutations, %</th>
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</thead>
<tbody>
<tr>
<td>SPRING-2</td>
<td>96</td>
<td>ATV/RTV (n = 411)</td>
<td>22 (5)</td>
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</tr>
<tr>
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<td></td>
<td>ABC/3TC/TDF (n = 411)</td>
<td>26 (7)</td>
<td>1 (RT185I)</td>
</tr>
<tr>
<td>SINGLE-2</td>
<td>96</td>
<td>ATV/3TC (n = 414)</td>
<td>19 (4)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DRV/3TC/TDF (n = 419)</td>
<td>33 (8)</td>
<td>1 (M61I)</td>
</tr>
<tr>
<td>FLAMINGO</td>
<td>344</td>
<td>ATV/RTV (n = 242)</td>
<td>2 (0.8)</td>
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<tr>
<td></td>
<td></td>
<td>DRV/RTV (n = 242)</td>
<td>4 (1.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

Prevalence of Drug Resistance in British Columbia

- HIV-1-infected persons age ≥19 years were included if they received ART through the BC Centre for Excellence.
- Increase in INSTI use from 10% of ART-treated persons in 2009 (540 raltegravir-treated) to 32% in 2015 (N=978 raltegravir, 500 elvitegravir and 1011 dolutegravir).
- In 2015, 8 patients developed INSTI resistance; 3 on DTG – 2 ART experienced (263K); 1 on first line ART 66I.

Elvitegravir/cobi/FTC/TAF
Pooled Week 48 HIV Drug Resistance in Phase 3 Trials

- Phase 3 trials (n=2287)
  - Treatment-naive (studies 104, 111, 106)
  - Virologically suppressed (studies 109 and 119)
  - Renal impairment (study 112)
  - HIV/HBV coinfected (study 249)
- E/C/TAF in adults (n=2237)
  - HIV RNA <50 copies/mL at week 48: 92%-100%
  - HIV-1 subtype or pretreatment RAMs did not affect response to treatment.
- Virologic failure with resistance data
  - HIV RNA level >400 copies/mL
  - 0.8% (18/2237)

RAMs: resistance-associated mutations.
Excluded: viremic patients who remained on study drug and later resuppressed HIV RNA <50 copies/mL without resistance.

Viral load Monitoring and Multiple Treatment Options

Viremic patients with multi-drug resistant HIV-1

Patients currently suppressed on therapy that have multi-drug resistant HIV-1
Resistance in the Developing World

- Second-line study: NNRTI/NRTI first line virologic failure – 15 countries – majority of participants from Africa or Asia
  - Baseline resistance - 492 participant samples

- 61% had at least 2 NRTI mutations
- 15% K65R or K70E and 13.4% had multinucleoside mutations (69 insertion or 151 complex)

Boyd, M et al Lancet 2013; 381: 2091–09
Published Online January 28, 2015 – Abstract 503

New Agents for Resistant HIV-1

- Integrase Inhibitors
  - Dolutegravir (approved)
  - GS-9883 (Phase III)
- N(t)RTI
  - TAF (approved)
  - Efavirenz (4′-ethynyl-2-fluoro-2′-deoxyadenosine)(Phase I-II)
- NNRTI
  - Doravirine (Phase III)

New Targets: e.g. LEDGF, combination entry, additional maturation sites, HIV-1 RNA processing

Antiretroviral Therapy: The Future


- ZDV monotherapy
- Triple Drug Therapy
- Long Acting Injectable?
- The Integrase Era
- Single Tablet Regimens
- The Integrase Era...