The Eras of the HIV Epidemic

1930-1980

1981-1986

1987-1995

1996-2005

2nd Gen. HAART

2006-

2011
Second Generation HAART Era: 2006-2011

2006: Disproportionate distribution of HIV

A global view of HIV infection
39.5 million people [34.1-47.1] living with HIV in 2006

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
Second Generation HAART Era: 2006-2011

2006: Gates and Clinton at International AIDS conference announce increased funding and in-country work.
### Second Generation HAART Era: 2006-2011

#### 2006: WHO revision of ART Guidelines

**Table 3. CD4 criteria for the initiation of ART in adults and adolescents**

<table>
<thead>
<tr>
<th>CD4 (cells/mm$^3$)</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>Treat irrespective of clinical stage [A-III]</td>
</tr>
<tr>
<td>200–350</td>
<td>Consider treatment and initiate before CD4 count drops below 200 cells/mm$^3$ [A-III]</td>
</tr>
<tr>
<td>&gt;350</td>
<td>Do not initiate treatment [A-III]</td>
</tr>
</tbody>
</table>

**Table 4. Recommendations for initiating ART in adults and adolescents in accordance with clinical stages and the availability of immunological markers**

<table>
<thead>
<tr>
<th>WHO clinical staging</th>
<th>CD4 testing not available</th>
<th>CD4 testing available</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do not treat [A-III]</td>
<td>Treat if CD4 count is below 200 cells/mm$^3$ [A-III]</td>
</tr>
<tr>
<td>2</td>
<td>Do not treat [B-III]</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Treat [A-III]</td>
<td>Consider treatment if CD4 count is below 350 cells/mm$^3$ and initiate ART before CD4 count drops below 200 cells/mm$^3$ [B-III]</td>
</tr>
</tbody>
</table>
Second Generation HAART Era: 2006-2011

2006: Benefit of treatment in developed nations

AIDS Drugs Have Saved 3 Million Years of Life in the United States

The Survival Benefits of AIDS Treatment in the United States

RP Walensky et al.
2006: CDC recommends routine opt-out HIV testing

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

For patients in all health-care settings

- HIV screening is recommended for patients in all health-care settings after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- Persons at high risk for HIV infection should be screened for HIV at least annually.
- Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
- Prevention counseling should not be required with HIV diagnostic testing or as part of HIV screening programs in health-care settings.
Second Generation HAART Era: 2006-2011

2006: 1st 2-Class STR (Single Tablet Regimen)
Atripla: 1st significant reduction in pill burden
Second Generation HAART Era: 2006-2011

2006: 10th PI Darunavir approved.

New Standard = high efficacy in treatment experienced patients

Clotet Lancet 2007; 369:1169
Second Generation HAART Era: 2006-2011

2006: Increased risk of osteoporosis

T. Brown. Lipodystrophy meeting. Dublin 2005
T. Brown, R. Qaqish: AIDS 2006; 20: 2165–2174
Second Generation HAART Era: 2006-2011

2006: Immune activation from microbial translocation

Published online: 19 November 2006 | doi:10.1038/nm1511

**Microbial translocation is a cause of systemic immune activation in chronic HIV infection**

Jason M Brenchley¹, David A Price¹, Timothy W Schacker², Tedi E Asher¹, Guido Silvestri³, Srinivas Rao³, Zachary Kazaz⁴, Ethan Bornstein¹, Olivier Lambotte⁵, Daniel Altmann⁶, Bruce R Blazar⁷, Benigno Rodriguez⁸, Leia Teixeira-Johnson⁸, Alan Landay⁹, Jeffrey N Martin¹⁰, Frederick M Hecht¹⁰, Louis J Picker¹¹, Michael M Lederman⁸, Steven G Deeks¹⁰ & Daniel C Douek¹

Chronic activation of the immune system is a hallmark of progressive HIV infection and better predicts disease outcome than plasma viral load, yet its etiology remains obscure. Here we show that circulating microbial products, probably derived from the gastrointestinal tract, are a cause of HIV-related systemic immune activation. Circulating lipopolysaccharide, which we used as an indicator of microbial translocation, was significantly increased in chronically HIV-infected individuals and in simian.
Second Generation HAART Era: 2006-2011

2006: Accumulation of resistance mutations with continuation of partially suppressive ARV regimen
CD4+ Count–Guided Interruption of Antiretroviral Treatment

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group

A. Opportunistic Disease or Death from Any Cause

- Hazard ratio, 2.6; 95% CI, 1.9–3.7; P<0.001

- Cumulative Probability of Event

- Months

- No. at Risk
  - Drug conservation
    - 2720
    - 2074
    - 1866
    - 1301
    - 1040
    - 870
    - 689
    - 540
    - 444
    - 372
    - 280
    - 162
  - Viral suppression
    - 2752
    - 2081
    - 1695
    - 1310
    - 1077
    - 906
    - 724
    - 572
    - 474
    - 388
    - 288
    - 173

B. Major Cardiovascular, Renal, or Hepatic Disease

- Hazard ratio, 1.7; 95% CI, 1.1–2.5; P=0.009

- Cumulative Probability of Event

- Months

- No. at Risk
  - Drug conservation
    - 2720
    - 2070
    - 1663
    - 1292
    - 1041
    - 867
    - 693
    - 543
    - 443
    - 375
    - 273
    - 157
  - Viral suppression
    - 2752
    - 2077
    - 1692
    - 1307
    - 1070
    - 899
    - 713
    - 563
    - 462
    - 380
    - 282
    - 165

Second Generation HAART Era: 2006-2011

2006: Immune restoration determines disease progression

Disease progression in patients with virological suppression in response to HAART is associated with the degree of immunological response.

- **CD4 Change from baseline:**
  - $\geq 25$ cells/ml
  - $< 25$ cells/ml

- **Absolute CD4 Level on HAART:**
  - $\geq 200$ cells/ml
  - $< 200$ cells/ml
Second Generation HAART Era: 2006-2011

2007: 1500 international delegates convene to discuss prevention and treatment in the field

2007 HIV/AIDS Implementers’ Meeting
Kigali, Rwanda – June 16–19, 2007
2008 HIV/AIDS Implementers’ Meeting: June 2008, Kampala, Uganda

Scaling Up Through Partnerships
Second Generation HAART Era: 2006-2011

2007: Provider-initiated routine HIV testing recommended internationally

Guidance on Provider-Initiated HIV Testing and Counselling in Health Facilities

World Health Organization
UNAIDS

HIV/AIDS Programme
Strengthening health services to fight HIV/AIDS
Second Generation HAART Era: 2006-2011

2007: International leaders revise pledge for ARV treatment of 5 million by 2010
Second Generation HAART Era: 2006-2011

2007: International vaginal micobicide trial halted for lack of efficacy
Second Generation HAART Era: 2006-2011

2007: Insulin resistance accompanies mitochondrial toxicity

**d4T Causes Insulin Resistance**

**Glucose Infusion Rate** Decreased With d4T

- Glucose Infusion Rate (mg/kg/minute)
- d4T: 0
- Placebo: 0
- $P = .04$

**Mitochondrial DNA** Decreased With d4T

- Mitochondrial DNA/Nuclear DNA Percent Change
- d4T: -80
- Placebo: 0
- $P = .005$
- $P = .9$

Fleishman A et al. 14th CROI; 2007; Los Angeles; Abstract 43.
Second Generation HAART Era: 2006-2011

2007: Lipoatrophy increases after $\geq 3$ years zidovudine

SWEET DEXA Substudy
Lipoatrophy by Duration ZDV Exposure

Proportion of Patients With Low Limb Fat by DEXA

<table>
<thead>
<tr>
<th>Years of ZDV Exposure at Baseline</th>
<th>0.7-1.8</th>
<th>1.9-2.9</th>
<th>3.0-4.5</th>
<th>4.6-9.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion</td>
<td>38%</td>
<td>38%</td>
<td>63%</td>
<td>67%</td>
</tr>
</tbody>
</table>

Moyle G et al. 9th ADRL; 2007; Sydney P12.
Second Generation HAART Era: 2006-2011

2007: Lipoatrophy worse with certain NRTIs

ACTG 5142 Metabolic Outcomes

Percent With Lipoatrophy by NRTI Groups (Week 96)

<table>
<thead>
<tr>
<th>NRTI Group</th>
<th>Weeks on Study</th>
<th>Percent Lipoatrophy (≥ 20% Loss)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>93</td>
<td>26%</td>
</tr>
<tr>
<td>LPV/r</td>
<td>133</td>
<td>16%</td>
</tr>
<tr>
<td>LPV/r + EFV</td>
<td>153</td>
<td>8%</td>
</tr>
<tr>
<td>ZDV</td>
<td>84</td>
<td>42%</td>
</tr>
<tr>
<td>TDF</td>
<td>117</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>136</td>
<td>9%</td>
</tr>
</tbody>
</table>

Second Generation HAART Era: 2006-2011

2007: PREDICT 1 Study confirms HLA-B*5701 association with ABC hypersensitivity reaction

Second Generation HAART Era: 2006-2011

2007: CD4 ≥800 after 7 years if ART initiated at CD4 ≥350

Gras JAIDS 2007 45:183-192
Second Generation HAART Era: 2006-2011

2007: 4 drugs no better than 3

ACTG 5095
Time to Virologic Response

Confirmed HIV RNA <200 copies/mL

- ZDV/3TC/ABC+EFV
- ZDV/3TC+EFV

No difference in probability of not failing among patients with HIV RNA >100,000 copies/mL.
Second Generation HAART Era: 2006-2011

2007: 1\textsuperscript{st} CCR5 Inhibitor Maraviroc
Second Generation HAART Era: 2006-2011

2007: VL suppression related to number of active ARV agents
Second Generation HAART Era: 2006-2011

2007: 1st INSTI Raltegravir: Rapid VL Suppression

Fully suppressive “Salvage” regimens available again

Second Generation HAART Era: 2006-2011

2006   2007   2008   2009   2010   2011

Four drugs no better than three
Second Generation HAART Era: 2006-2011

2008: HIV and AIDS continue to rise in Japan

Figure 2. Nationality and gender of HIV cases and AIDS patients, 1985-2008, Japan

Second Generation HAART Era: 2006-2011

2008: International gains in ART: Steady but below target

Number of people receiving antiretroviral therapy
(end of year, lower- and middle-income countries)
Second Generation HAART Era: 2006-2011

2008: International AIDS conference: Focus on community involvement
Second Generation HAART Era: 2006-2011

2008: Increasing global perinatal transmission prevention

Estimate of the annual number of infant infections averted through the provision of antiretroviral prophylaxis to HIV-positive pregnant women, globally, 1996–2008.
Second Generation HAART Era: 2006-2011

2008: Persistent increase in US HIV “incidence”: 54,000 new infections annually
Second Generation HAART Era: 2006-2011

2008: National HIV care quality measures approved
### Second Generation HAART Era: 2006-2011

#### 2008: National HIV care quality measures approved

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Retention in care</td>
<td>two visits/year</td>
</tr>
<tr>
<td>2.</td>
<td>CD4 measurement</td>
<td>twice/year</td>
</tr>
<tr>
<td>3.</td>
<td>GC / CT screening</td>
<td>once/year</td>
</tr>
<tr>
<td>4.</td>
<td>Syphilis screening</td>
<td>once/year</td>
</tr>
<tr>
<td>5.</td>
<td>Injection drug use screening</td>
<td>once/year</td>
</tr>
<tr>
<td>6.</td>
<td>High-risk sex screening</td>
<td>once/year</td>
</tr>
<tr>
<td>7.</td>
<td>Tuberculosis screening</td>
<td>once/year</td>
</tr>
<tr>
<td>8.</td>
<td>Hepatitis B screening</td>
<td>once ever</td>
</tr>
<tr>
<td>9.</td>
<td>Hepatitis C screening</td>
<td>once ever</td>
</tr>
<tr>
<td>10.</td>
<td>Influenza immunization</td>
<td>annually</td>
</tr>
<tr>
<td>11.</td>
<td>Pneumococcal immunization</td>
<td>once</td>
</tr>
<tr>
<td>12.</td>
<td>Hepatitis B vaccination</td>
<td>ordered</td>
</tr>
<tr>
<td>13.</td>
<td>Hepatitis B vaccination</td>
<td>completed</td>
</tr>
<tr>
<td>14.</td>
<td>PCP prophylaxis</td>
<td>if CD4 &lt;200</td>
</tr>
<tr>
<td>15.</td>
<td>ART prescribed</td>
<td>if appropriate</td>
</tr>
<tr>
<td>16.</td>
<td>Viral suppression</td>
<td>system level</td>
</tr>
<tr>
<td>17.</td>
<td>Viral suppression</td>
<td>provider level</td>
</tr>
</tbody>
</table>
Second Generation HAART Era: 2006-2011

2008: 4th NNRTI: Etravirine:
High VL suppression rate in DUET trial

Katlama AIDS 2009; 23:2299
2008: Evaluating number of baseline mutations becomes new standard in treatment experienced.

### ETR and DRV Mutations

High response rates in pts with ≤ 3 combined ETR + DRV mutations at Wk 24.

<table>
<thead>
<tr>
<th>ETR mutations, n</th>
<th>VL&lt;50 c/mL, % (n/N)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>&gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Darunavir</td>
<td></td>
<td>78 (7/9)</td>
<td>67 (8/12)</td>
<td>100 (3/3)</td>
<td>67 (2/3)</td>
<td>0 (0/1)</td>
</tr>
<tr>
<td>Mutations, n</td>
<td></td>
<td>83 (36/44)</td>
<td>71 (27/38)</td>
<td>93 (13/14)</td>
<td>57 (4/7)</td>
<td>40 (2/5)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>73 (30/41)</td>
<td>75 (18/24)</td>
<td>56 (9/16)</td>
<td>29 (2/7)</td>
<td>17 (1/6)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>78 (31/40)</td>
<td>50 (12/24)</td>
<td>45 (9/20)</td>
<td>60 (3/5)</td>
<td>30 (3/10)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>63 (17/27)</td>
<td>35 (8/23)</td>
<td>27 (3/11)</td>
<td>27 (3/11)</td>
<td>0 (0/5)</td>
</tr>
<tr>
<td>&gt;3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2008: ARV CHARTER score correlates with CNS VL

Second Generation HAART Era: 2006-2011

2008: HIV persistence in GALT

Persistence of HIV in Gut-Associated Lymphoid Tissue despite Long-Term Antiretroviral Therapy

Figure 2. Frequency of HIV proviral DNA in resting and activated CD4+ T cells sorted by fluorescence-activated cell sorter analysis (FACS) and CD8-depleted single cell suspensions from gut-associated lymphoid tissue (GALT) (term 714 • JID 2008:197 (1 March) • Chun et al. unpublished).
Second Generation HAART Era: 2006-2011

2008: Durable persistence of viremia on suppressive antiretroviral therapy

Low-level viremia persists for at least 7 years in patients on suppressive antiretroviral therapy.
Second Generation HAART Era: 2006-2011

2008: SMART: Continuous ART superior to interrupted ART

Emery J Inf Dis 2008;197:1133-1144; Gill CID 2010;50:98-105
Genetic and Immunologic Heterogeneity among Persons Who Control HIV Infection in the Absence of Therapy

Conclusions. Elite controllers are a distinct group, even when compared to persons with low level viremia, but they exhibit marked genetic and immunologic heterogeneity. Even low-level viremia among HIV controllers was associated with measurable T cell dysfunction, which has implications for current prophylactic vaccine strategies.
Second Generation HAART Era: 2006-2011

2008: Berlin patient “functionally cured” of HIV


From the Charité – Medical University of Berlin, Germany

Barring the Door | How a mutation can protect against HIV

With CCR5
To enter cells, one thing that most HIV strains must do is bind to CCR5, a molecule that protrudes from the cells surface.

Without CCR5
Some people are born with a mutation that prevents CCR5 from appearing on their cells, making them resistant to HIV. Some experimental gene therapy approaches aim to mimic this mutation in AIDS patients.

CROI 2008 Abstract 719
Second Generation HAART Era: 2006-2011
Second Generation HAART Era: 2006-2011

2009: Pope warns against condom use:
WHO states Pope's comments “dangerous”
Second Generation HAART Era: 2006-2011

2009: India lifts ban against homosexuality
Second Generation HAART Era: 2006-2011

2009: US allows government funding of needle exchange programs
Second Generation HAART Era: 2006-2011

2009: HIV Vaccine still elusive

US NIAID HIV Vaccine Trial Network
Second Generation HAART Era: 2006-2011

2009: Early ART beneficial during acute OIs

Figure 3. Time to AIDS progression or death. HR = 0.53 Early versus Deferred ART (95%CI 0.30-0.92 p = 0.023).

Second Generation HAART Era: 2006-2011

2009: Residual viremia not reducible with current ARVs

Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy

PNAS June 9, 2009 vol. 106 no. 23 9403-9408
2009: CD4 restoration better with earlier ARV treatment

Incomplete Peripheral CD4⁺ Cell Count Restoration in HIV-Infected Patients Receiving Long-Term Antiretroviral Treatment

The time from initiation of HAART to achievement of a CD4⁺ cell count $>500$ cells/mm³, estimated using Kaplan-Meier techniques.

- N=216
- N=76
- N=74


Clinical Infectious Diseases
### Second Generation HAART Era: 2006-2011

#### 2009: Survival benefit when ART started at CD4 >500

<table>
<thead>
<tr>
<th></th>
<th>CD4 350 – 500</th>
<th></th>
<th>CD4 &gt;500</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR of Death (95% CI)</td>
<td>P Value</td>
<td>RR of Death (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Deferred ART</td>
<td>1.69 (1.26-2.26)</td>
<td>&lt;0.001</td>
<td>1.94 (1.37-2.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NA-ACCORD, Kitahata NEJM 2009;360:1815-1826
Second Generation HAART Era: 2006-2011

2010: US lifts 22 year HIV travel ban
Followed by South Korea, China and Namibia

HIV Travel Ban Lifted By President Obama

[Image of flags from South Korea, China, and Namibia]
Antiretroviral Treatment of Adult HIV Infection
2010 Recommendations of the International AIDS Society–USA Panel
### 2010: WHO guidelines closer to US guidelines

#### Table 5. When to start antiretroviral therapy

<table>
<thead>
<tr>
<th>Target population</th>
<th>2010 ART guideline</th>
<th>2006 ART guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+ asymptomatic ARV-naive individuals</td>
<td>CD4 ≤ 350 cells/mm³</td>
<td>CD4 ≤ 200 cells/mm³</td>
</tr>
<tr>
<td></td>
<td>WHO clinical stage 2 if CD4 ≤ 350 cells/mm³ OR WHO clinical stage 3 or 4 irrespective of CD4 cell count</td>
<td>WHO stage 2 or 3 and CD4 ≤ 200 cells/mm³</td>
</tr>
<tr>
<td></td>
<td>WHO stage 3 if CD4 not available</td>
<td>WHO stage 3 irrespective of CD4 cell count</td>
</tr>
<tr>
<td>HIV+ symptomatic ARV-naive individuals</td>
<td>Consider treatment for WHO clinical stage 3 and CD4 cell count between 200 and 350 cells/mm³</td>
<td>Consider treatment for WHO clinical stage 3 and CD4 cell count</td>
</tr>
<tr>
<td>HIV+ pregnant women</td>
<td>CD4 ≤ 350 cells/mm³ irrespective of clinical symptoms OR WHO clinical stage 3 or 4 irrespective of CD4 cell count</td>
<td>WHO stage 1 and 2 and CD4 ≤ 200 cells/mm³</td>
</tr>
<tr>
<td></td>
<td>WHO stage 3 and CD4 ≤ 350 cells/mm³</td>
<td>WHO stage 4 irrespective of CD4 cell count</td>
</tr>
<tr>
<td>HIV/TB coinfection ARV-naive individuals</td>
<td>Presence of active TB disease, irrespective of CD4 cell count</td>
<td>Presence of active TB disease and CD4 ≤ 350 cells/mm³</td>
</tr>
<tr>
<td></td>
<td>ART Initiation can be delayed if CD4 ≤ 200 cells/mm³</td>
<td>ART Initiation can be delayed if CD4 ≤ 200 cells/mm³</td>
</tr>
<tr>
<td>HIV/HBV coinfection ARV-naive individuals</td>
<td>Individuals who require treatment for their HBV infection, irrespective of CD4 cell count</td>
<td>No specific recommendation</td>
</tr>
</tbody>
</table>
Conclusion: Among people who survived for several years or more after an AIDS diagnosis, we observed high risks of AIDS-defining cancers and increasing incidence of anal cancer and Hodgkin lymphoma.

Arch Intern Med. 2010;170(15):1337-1345
Second Generation HAART Era: 2006-2011

2010: Early ART during TB treatment increases survival and IRIS

CAMELIA Study: Blanc, 18th IAC 2010, Abstract THLBB106.
Second Generation HAART Era: 2006-2011

2010: Improved survival with earlier initiation even in resource limited settings

Severe NEJM 2010 363:257-265
Second Generation HAART Era: 2006-2011

2010: Lower rate of resistance when ART started early

Uy, JAIDS 2009 51:450. Lodwick ArchIntMed 2010;170:410
Second Generation HAART Era: 2006-2011

2010: CCR5 enhanced trofile for maraviroc use

Maraviroc versus Efavirenz in ARV-Naive Subjects

- JID 2010:201 (15 March) • 803
Second Generation HAART Era: 2006-2011

2010: 4th Gen Ab/Ag test allows earlier HIV diagnosis
Second Generation HAART Era: 2006-2011

2010: INSTI intensification will not eradicate HIV

Figure 2. Human immunodeficiency virus type 1 (HIV-1) RNA levels for all time points for all 9 evaluable participants. Each set of colored symbols represents HIV-1 RNA values obtained for the indicated patient during

McMahon D, CID 2010, 50 (6): 912-919
Second Generation HAART Era: 2006-2011

2010: PrEP Reduces MSM HIV Acquisition

The NEW ENGLAND JOURNAL of MEDICINE

Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

iPrEX study shows TDF-FTC reduces HIV infection rate by 44%
Second Generation HAART Era: 2006-2011

2011: cART Prevents Heterosexual HIV Transmission

HPTN 052
A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy Plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 in Serodiscordant Couples

cART leads to 96% reduced risk of transmission to uninfected partners
Second Generation HAART Era: 2006-2011

2011: PrEP Prevents Heterosexual HIV Transmission and Acquisition

TDF-2: TDF-FTC reduces HIV infection rate by 78% on treatment

Failure Probability

Time to Seroconversion (ITT Analysis)

Second Generation HAART Era: 2006-2011

2011: Bone density change differs among ARVs

McComsey, J Inf Dis 2011; 203:1791.
Second Generation HAART Era: 2006-2011

2011: Older aged patients do better when HAART initiated at higher CD4

BMJ, November 2011, 343
Second Generation HAART Era: 2006-2011

2011: Minority Resistance Variants (MV)
Increase risk of initial failure

Li, *JAMA* 2011; 305:1327.
Second Generation HAART Era: 2006-2011

2011: NNRTI NVP-extended release

VERXVE: PK Sub-study at Day 28: Results

VERXVE: Sustained Virologic Response at Week 48
(VL <50 copies/mL, FAS)

**VERXVE: PK Sub-study at Day 28: Results**

- 200ng Viramune IR BID (N=25)
- 400ng Viramune XR QD (N=24)

**VERXVE: Sustained Virologic Response at Week 48**

- Viramune IR: 75.89% (384/506)
- Viramune XR: 80.99% (419/505)

Adjusted difference: 4.12% in favour of Viramune XR, with 95% CI of (-0.11, 9.31)

Viramune XR shows non-inferiority to Viramune IR within pre-specified margin of -10%

Virologic response was independent of age, gender, race or geographic region

FAS = Full analysis set
Second Generation HAART Era: 2006-2011

2011: 5th NNRTI: Rilpivirine receives selective approval

ECHO and THRIVE: VL <50 copies/mL by baseline VL (ITT-TLOVR)

- NRTI background had no effect on virologic response
- No differences between treatment groups in virologic response by gender, region or race

Cohen C, et al. XVIIIth IAC 2010; Abstract THLB205
Second Generation HAART Era: 2006-2011

2011: 2\textsuperscript{nd} 2-class Single Tablet Regimen: Complera
### Evolution of HIV treatment paradigms

<table>
<thead>
<tr>
<th>ART</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>Mono-NRTI and Dual-NRTI</th>
<th>Early 3-drug HAART</th>
<th>Boosted Prot.Inh.</th>
<th>“Salvage” HAART</th>
<th>High VL suppression success rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential Mono-Tx</td>
<td>1994</td>
<td>1998</td>
<td>SQV&lt;sub&gt;sgc&lt;/sub&gt;</td>
<td>RTV&lt;sub&gt;idv&lt;/sub&gt;</td>
<td>SQV&lt;sub&gt;ngc&lt;/sub&gt;</td>
<td>ATV&lt;sub&gt;apv&lt;/sub&gt;</td>
<td>DRV&lt;sub&gt;drv&lt;/sub&gt;</td>
<td>MVC&lt;sub&gt;r&lt;/sub&gt;</td>
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<tr>
<td>CD4 &lt;500</td>
<td>CD4 &lt;200</td>
<td>CD4 &lt;500, opt. &gt;500</td>
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**Table:**
- **NRTI:** AZT, ddi, d4T, 3TC, ABC, TDF, FTC, ddI-EC, Epzicom, Combivir, Trizivir, Truvada.
- **NNRTI:** ddC, 3TC, ddI.
- **PI:** NFV, APV, ATV, TPV, SQV, LPv, DRV.
- **Mono-NRTI and Dual-NRTI:** NVP, DLV, NVP<sup>apv</sup>, DRV<sup>apv</sup>, T-20, MVC, RAL.
- **ART** strategies include Sequential Mono-Tx, Mono-NRTI, and 3-drug HAART.
- **“Salvage” HAART** with high VL suppression success rates.
- **CD4 counts:** CD4 <500, CD4 <200, CD4 <500, opt. >500.