Twenty Years of HAART: Landmarks and Lessons

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Professor of Clinical Medicine
UCSD Owen Clinic
Landmark and Lessons

Landmarks

• Pre-HAART (1987 – 1996)
  • ACTG 076 and PMTCT (1994)
• HAART (1996 Vancouver)
• Viral load quantification & viral dynamics (1996)
• PK boosting of PIs (1997 – 1999)
• HIV resistance testing & adherence monitoring (2000)
• Transmitted Drug Resistance
• New drug classes
• TasP (2011)
• PrEP
• Back to “Hit hard, hit early” (2015)

Lessons

• Premature therapeutic optimism (1995)
  • “Hit hard, hit early”
• Not cost-effective to provide HAART in Sub-Saharan Africa (1996 – 2000)
• Toxicity-Efficacy Tradeoffs
• Inflammation-Aging
• Clinical trial casualties
• AIDS Activism
THE EFFICACY OF AZIDOTHYMIDINE (AZT) IN THE TREATMENT OF PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX

A Double-Blind, Placebo-Controlled Trial

MARGARET A. FISCHL, M.D., DOUGLAS D. RICHMAN, M.D., MICHAEL H. GRIECO, M.D., J.D.,
MICHAEL S. GOTTLIEB, M.D., PAUL A. VOLBERDING, M.D., OSCAR L. LASKIN, M.D., JOHN M. LEEDOM, M.D.,
JEROME E. GROOPMAN, M.D., DONNA MILDVAN, M.D., ROBERT T. SCHOOLEY, M.D.,
GEORGE G. JACKSON, M.D., DAVID T. DURACK, M.B., D.PHIL., DANNIE KING, PH.D.,
AND THE AZT COLLABORATIVE WORKING GROUP

Figure 1. Proportion of Patients in Whom Opportunistic Infections Developed during the Study (Kaplan–Meier Product–Limit Method). The left panel shows infection among patients with AIDS who were receiving AZT or placebo (PCB), and the right panel shows infection among those with AIDS-related complex (ARC).
HIV with Reduced Sensitivity to Zidovudine (AZT) Isolated During Prolonged Therapy

Larder et al. Science. 1989 Mar 31;243(4899):1731-4
Effect of Stage of Disease and Drug Dose on Zidovudine Susceptibilities of Isolates of Human Immunodeficiency Virus

Douglas D. Richman, *Janet M. Grimes, and *Stephen W. Lagakos

Departments of Pathology and Medicine, University of California San Diego and VA Medical Center, San Diego, California and *Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts
Detection of mutations associated with zidovudine resistance in human immunodeficiency virus by use of the polymerase chain reaction

Figure 4. Cumulative proportion of individuals with mutation at each of four codons of human immunodeficiency virus reverse transcriptase after initiation of zidovudine.

Figure 5. Relation of susceptibility of isolates of human immunodeficiency virus to number of mutations at codons 70, 215, and 219 of reverse transcriptase gene. Natural log (ln) IC$_{50}$ for each
Figure 1. Kaplan-Meier Plots of the Probability of HIV Transmission, According to Treatment Group.

The estimated percentages of infants infected at 72 weeks are shown with 95 percent confidence intervals. The numbers of infants at risk at 24, 48, and 72 weeks are shown below the figure.
David Ho: “Time to hit HIV, early and hard” (1995)

- But not in 1995
  - Concorde Study
  - ACTG 019

Concorde Trial: Immediate vs. Deferred ZDV in Symptom-free HIV Patients

Figure 3: Kaplan-Meier plots for all cause mortality (A), time to AIDS or death (B), time to ARC, AIDS or death (C), and time to a reduction in CD4 count to less than half of the baseline value or AIDS or death (3b plus the CD4 endpoint) (D)

*Lancet.* 1994 Apr 9;343(8902):871-81
IMMEDIATE WITH DEFERRED ZIDOVUDINE THERAPY FOR ASYMPTOMATIC HIV-INFECTED ADULTS WITH CD4 CELL COUNTS OF 500 OR MORE (ACTG 019)

Decay characteristics of HIV-1-infected compartments during combination therapy

Perelson et al. Nature. 1997 May 8;387(6629):188-91
Decay of circulating virus & infected cells

Figure 3. Decay of circulating virus and infected cells after initiation of suppressive antiviral therapy. These results imply the presence of at least four classes of HIV-infected cells: productively infected, a second class, perhaps macrophages, with a half-life of ~2 wk; latently infected resting CD4 cells, with a half-life of ~6 mo; and long-lived DNA positive cells, most of which are nonproductive. A fourth class of infected cells, inferred to have an approximately infinite half-life, is not shown. (Figure modified from Fauci and Desrosiers 1997.)

Tri-exponential model of predicted viral decay (weeks 0–72), using single-copy assay data.

Raltegravir combination therapy

Adriana Andrade et al. J Infect Dis. 2013;infdis.jit272

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HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time

Summary of Dual Nucleoside Potential: 1996

Table 1.—Results of Selected Recent Controlled Clinical Trials of Nucleoside Analogue: Studies With 250 Patients or More Observed for 48 Weeks or More

<table>
<thead>
<tr>
<th>Regimen*</th>
<th>No. of Studies (References)</th>
<th>Approximate No. of Patients</th>
<th>Maximum CD4+ Cell Count Increase, ×10^9/L†</th>
<th>Maximum HIV RNA Reduction, log_{10} Copies/mL†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials of initial therapy in antiretroviral-naive subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine/didanosine</td>
<td>3 (12, 27, 33-35)</td>
<td>1000</td>
<td>0.085</td>
<td>1.4</td>
</tr>
<tr>
<td>Zidovudine/zalcitabine</td>
<td>3 (12, 27, 33-35)</td>
<td>1000</td>
<td>0.085</td>
<td>1.1</td>
</tr>
<tr>
<td>Didanosine</td>
<td>1 (12, 33)</td>
<td>250</td>
<td>0.040</td>
<td>0.8</td>
</tr>
<tr>
<td>Zidovudine/lamivudine</td>
<td>2 (24, 36, 107)</td>
<td>300</td>
<td>0.085</td>
<td>1.7</td>
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<tr>
<td>Trials in antiretroviral-experienced patients†</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine/didanosine</td>
<td>3 (12, 33-35, 108)</td>
<td>1000</td>
<td>0.040</td>
<td>1.1</td>
</tr>
<tr>
<td>Zidovudine/zalcitabine</td>
<td>3 (12, 22, 33-35)</td>
<td>800</td>
<td>0.020</td>
<td>0.9</td>
</tr>
<tr>
<td>Didanosine</td>
<td>1 (12, 33)</td>
<td>350</td>
<td>0.035</td>
<td>0.7</td>
</tr>
<tr>
<td>Zidovudine/lamivudine</td>
<td>2 (41, 56, 109)</td>
<td>275</td>
<td>0.032</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Carpenter et al. JAMA. 1996 Jul 10;276(2):146-54
HIV viral load markers in clinical practice: 1996

Fig. 3 Composite of plasma HIV RNA and CD4+ cell count responses among a group of patients receiving three different antiretroviral regimens: zidovudine monotherapy (ZDV, 600 mg/day; solid lines), zidovudine plus lamivudine (ZDV/3TC, 600 mg/day, 300 mg/day, respectively; long-dashed lines), and the protease inhibitor, indinavir (MK-639, 2400 mg/day; short-dashed lines). All patients were naive to their respective treatment regimens. For each treatment group, the relative HIV RNA and CD4+ count treatment responses appear inversely proportional, although individual exceptions to this association exist.

Clinical Trial Results in Early HAART Era: Percent HIV Viral Load <50 at 48 weeks (ITT)
Pharmacokinetic enhancement of PI Exposure: 1997

Pharmacokinetic enhancement of SQV Exposure: 1997, 1999

Cameron et al. AIDS. 1999 Feb 4;13(2):213-24
Clinical Trial Results in Boosted-PI HAART Era: Percent HIV Viral Load <50 at 48 weeks (ITT)
**First HIV Resistance Testing Guidelines: 2000**

**Table 2. Summary of Recommendations for Resistance Testing, Based on Available Data and Expert Opinion**

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Recommendation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary HIV infection</td>
<td>Consider testing†</td>
<td>Detect transmission of drug-resistant virus; modify therapy to optimize response and maintain HIV-specific immune responses</td>
</tr>
<tr>
<td>Established HIV infection‡</td>
<td>Consider testing</td>
<td>Detect prior transmission of drug-resistant HIV although this may not always be possible with current tests</td>
</tr>
<tr>
<td>First regimen failure§</td>
<td>Recommend testing</td>
<td>Document drug(s) to which there is resistance</td>
</tr>
<tr>
<td>Multiple regimen failures§</td>
<td>Recommend testing</td>
<td>Optimize the number of active drugs in the next regimen; exclude drugs to which response is unlikely</td>
</tr>
</tbody>
</table>

*HIV indicates human immunodeficiency virus.*  
†Therapy should not be delayed while waiting for resistance testing results.  
‡In untreated established infection, wild-type virus may replace drug-resistant quasispecies over time. Drug resistance results should thus be interpreted with caution.  
§The results are most reliable for drugs that are being taken by the patient at the time of testing.

Early Adoption of HIV Resistance Testing: San Diego County (2000)

Mathews et al. AIDS Patient Care STDS. 2002 Jul;16(7):337-48

Figure 1. Adherence to antiretroviral therapy and virologic failure.

The degree of adherence was significantly associated with risk for virologic failure ($P < 0.001$). Adherence of 95% or greater was associated with the lowest incidence of virologic failure.


C. Mean Change from Baseline Plasma Viral Load, by MEMS Therapeutic Coverage Category

D. Mean Change in Plasma Viral Load, by Self-reported Adherence Score Category

Mathews et al. AIDS Patient Care STDS. 2002 Apr;16(4):157-72

Figure 1. Mortality and Frequency of Use of Combination Antiretroviral Therapy Including a Protease Inhibitor among HIV-Infected Patients with Fewer Than 100 CD4+ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.

Figure 2. Rates of Cytomegalovirus Infection, Pneumocystis carinii Pneumonia, and Mycobacterium avium Complex Disease among HIV-Infected Patients with Fewer Than 100 CD4+ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.

Outcomes of Care

Owen Clinic Death Rates (per 100 p-yrs) by Year of Entry
(Npatients=6233, Ndeaths=2001)
Letting them die in Sub-Saharan Africa: 1996-2000

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>N/a</td>
<td>Yes</td>
<td>1-99</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>N/a</td>
<td>Yes</td>
<td>1-43</td>
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<td>No</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>N/a</td>
<td>Yes</td>
<td>4-7</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>N/a</td>
<td>Yes</td>
<td>1-731</td>
</tr>
<tr>
<td>No</td>
<td>Yes?</td>
<td>No</td>
<td>No</td>
<td>N/a</td>
<td>Yes</td>
<td>12</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>N/a</td>
<td>Yes</td>
<td>18-22</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>N/a</td>
<td>Yes</td>
<td>2-68</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>N/a</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>No</td>
<td>?</td>
<td>No</td>
<td>?</td>
<td>N/a</td>
<td>Yes</td>
<td>77-1230</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>169-288</td>
</tr>
<tr>
<td>No</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>1100-1800</td>
</tr>
</tbody>
</table>

Reading from left to right, answers to the seven questions included in the framework are suggested, in the order in which they should be asked. ARV=antiretroviral therapy. MTCT=mother-to-child transmission. TB=tuberculosis. VCT=voluntary counselling and testing. N/a=not applicable.

Table 6: Economic factors affecting priority of health interventions for public funding

Letting them die in Sub-Saharan Africa: 1996-2000

• “Data on the cost-effectiveness of HIV prevention in sub-Saharan Africa and on highly active antiretroviral therapy (HAART) indicate that prevention is at least 28 times more cost effective than HAART. We aim to show that funding HAART at the expense of prevention means greater loss of life.”


• “Public health is purchasable . . . A community can determine its own death rate . . . No duty of society . . . Is paramount to this obligation to attack the removable causes of disease.” (Herman Biggs, New York Commissioner of Health, 1913)

• “Public health is purchasable, as has been proved in the past when aroused public interest has stamped out plague after plague which once ravaged the population . . . ” (Thomas Paran, US Surgeon General, 1936)

Affordable prices

Annual cost per person for triple therapy in Africa (US$)

- Drug Access Initiative
- Domestic production
- Accelerated access initiative
- February-April 2001 offers
ART Cost and Scale-up Relationship (Uganda)

FIGURE 5.1 TRENDS IN THE COST OF ANTIRETROVIRAL (ARV)

Global ART Treatment Coverage

![Bar chart showing estimated percentage of antiretroviral treatment (ART) coverage for children and adults globally.](image)

**Figure 5.2** Estimated percentage antiretroviral treatment (ART) coverage based on WHO 2010 guidelines.

Figure 1: Estimated cumulative probability of death in HAART programmes in low-income and high-income countries. Vertical bars are 95% CIs.
Mortality in patients with HIV-1 infection starting antiretroviral therapy in South Africa, Europe, or North America

Evolution of CD4 antiretroviral therapy initiation threshold according to the DHHS HIV guidelines.

Transmitted Drug Resistance: Spain

Transmitted Drug Resistance: La Coruña

Fig. 4. Rates of TDR mutations in periods 2004–2008 and 2009–2013.

Survival of Persons with and without HIV Infection in Denmark, 1995–2005


Figure Legend:
Survival from age 25 years. Cumulative survival curve for HIV-infected persons (without hepatitis C coinfection) and persons from the general population. Persons with HIV infection are divided into 3 calendar periods of observation. Dashed lines indicate 95% CIs. HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy.
HIV Treatment as Prevention (TasP)


HR 0.04 (95% CI: 0.01 - 0.27)
# PrEP: TDF/FTC by Risk Group

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TDF-FTC Events Total</th>
<th>placebo Events Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Heterosexual group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baeten 2012</td>
<td>13 1579</td>
<td>52 1584</td>
<td>23.9%</td>
</tr>
<tr>
<td>Thigpen 2012</td>
<td>9 601</td>
<td>24 599</td>
<td>20.6%</td>
</tr>
<tr>
<td>Van Damme 2012</td>
<td>33 1024</td>
<td>35 1032</td>
<td>27.0%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>3204</td>
<td>3215</td>
<td>71.5%</td>
</tr>
<tr>
<td>Total events</td>
<td>55</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.51; Chi² = 12.85, df = 2 (P = 0.002); I² = 84%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 1.75 (P = 0.08)</td>
<td></td>
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</tr>
</tbody>
</table>

| **1.1.2 MSM group** | | | |
| Grant 2010 | 36 1251 | 64 1248 | 28.5% | 0.56 [0.38, 0.84] |
| **Subtotal (95% CI)** | **1251** | **1248** | **28.5%** | **0.56 [0.38, 0.84]** |
| Total events | 36 | 64 | |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 2.83 (P = 0.005) |

| **Total (95% CI)** | 4455 | 4463 | 100.0% | **0.49 [0.28, 0.85]** |
| Total events | 91 | 175 | |
| Heterogeneity: Tau² = 0.24; Chi² = 12.85, df = 3 (P = 0.005); I² = 77% |
| Test for overall effect: Z = 2.52 (P = 0.01) |
| Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.68); I² = 0% |

### PrEP: TDF/FTC by Gender

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.2.1 Women</strong></td>
<td></td>
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</tr>
<tr>
<td>Baeten 2012</td>
<td>9</td>
<td>566</td>
<td>28</td>
<td>619</td>
<td>40.7%</td>
<td>0.35 [0.17, 0.74]</td>
<td></td>
</tr>
<tr>
<td>Thigpen 2012</td>
<td>7</td>
<td>274</td>
<td>14</td>
<td>270</td>
<td>28.6%</td>
<td>0.49 [0.20, 1.20]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>840</strong></td>
<td><strong>693</strong></td>
<td><strong>889</strong></td>
<td><strong>69.3%</strong></td>
<td></td>
<td><strong>0.40 [0.23, 0.71]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>16</td>
<td>42</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Heterogeneity:</strong> Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%</td>
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<tr>
<td><strong>Test for overall effect:</strong> Z = 3.12 (P = 0.002)</td>
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</tr>
<tr>
<td><strong>1.2.2 Men</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baeten 2012</td>
<td>4</td>
<td>1010</td>
<td>24</td>
<td>959</td>
<td>20.6%</td>
<td>0.16 [0.06, 0.45]</td>
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<tr>
<td>Thigpen 2012</td>
<td>2</td>
<td>327</td>
<td>10</td>
<td>329</td>
<td>10.1%</td>
<td>0.20 [0.04, 0.91]</td>
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</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1337</strong></td>
<td><strong>30.7%</strong></td>
<td><strong>1288</strong></td>
<td><strong>30.7%</strong></td>
<td></td>
<td><strong>0.17 [0.07, 0.41]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>6</td>
<td>34</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Heterogeneity:</strong> Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%</td>
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<tr>
<td><strong>Test for overall effect:</strong> Z = 4.00 (P &lt; 0.0001)</td>
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<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2177</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>2177</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>0.31 [0.19, 0.50]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>22</td>
<td>76</td>
<td></td>
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</tr>
<tr>
<td><strong>Heterogeneity:</strong> Tau² = 0.01; Chi² = 3.07, df = 3 (P = 0.38); I² = 2%</td>
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<tr>
<td><strong>Test for overall effect:</strong> Z = 4.74 (P &lt; 0.00001) &amp; Test for subgroup differences:** Chi² = 2.63, df = 1 (P = 0.10), I² = 62.0%</td>
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</tbody>
</table>

Okwundu et al. [Cochrane Database Syst Rev.](http://www.cochranelibrary.com) 2012 Jul 11;7:CD007189
Back to “Hit Hard and Hit Early” (2015)

1. START study

2. TEMPRANO


Landmark and Lessons

**Landmarks**
- Pre-HAART (1987 – 1996)
  - ACTG 076 and PMTCT (1994)
- HAART (1996 Vancouver)
- Viral load quantification & viral dynamics (1996)
- HIV resistance testing & adherence monitoring (2000)
- Transmitted Drug Resistance
- New drug classes
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**Lessons**
- Premature therapeutic optimism (1995)
  - “Hit hard, hit early”
- Not cost-effective to provide HAART in Sub-Saharan Africa (1996 – 2000)
- Toxicity-Efficacy Tradeoffs
- Inflammation-Aging
- Clinical trial casualties
- AIDS Activism
Identifying distinct steps in HIV-1 life cycle as potential or current target for antiretroviral drugs.


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