Time Trends in Primary HIV-1 Drug Resistance Among Recently Infected Persons

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Primary HIV-1 (human immunodeficiency virus type 1) resistance to antiretroviral drugs has been reported.1-10 The proportion of recently infected individuals who acquire HIV-1 that is resistant to 2 or more classes of antiretroviral drugs is 2.7% (1/37) in San Francisco,4 2.9% (2/or more classes of antiretroviral drugs is resistance to all available classes of antiretroviral therapy. Genotypic resistance to 2 or more classes of drugs increased from 2.5% to 12 (13.2%) (P = .004), but only 1 infection (1.2%) in the latter period was resistant to all 3 classes of agents (P = .58). Primary phenotypic resistance decreased for NRTIs from 21% to 6.2% (P = .03) and increased for NNRTIs from 0% to 8 (9.9%) (P = .02). Phenotypic resistance increased for protease inhibitors from 2.6% to 6.2% (P = .32). Median time to virologic suppression (<500 copies/mL) during therapy was 12 weeks for patients with genotypic evidence of resistance compared with 5 weeks for patients with drug-sensitive infections (P = .02).

Conclusions The frequency of primary resistance to NNRTIs is increasing, although resistance to all available classes of antiretroviral therapy remains rare. Genotypic resistance testing in recently infected persons predicts time to viral suppression during therapy.

Methods

Study Population

Consecutive participants with evidence of acute or recent HIV-1 infection in the San Francisco Bay area were enrolled in the Options Project at San Francisco General Hospital. Participants were recruited through referrals from physicians, HIV-1 testing and counseling sites, community-based organizations, community health centers, and self-referral. Individuals at risk for HIV-1 infection and complaining of 2 or more symptoms of acute infection and asymptomatic individuals with recent receptive anal sex with a known
HIV-1–infected partner were eligible to receive laboratory screening for acute HIV-1 infection.

Participants were eligible for this study if they met 1 of the following criteria for recent HIV infection at specimen collection for resistance testing: (1) detectable HIV-1 RNA in blood plasma and a negative or indeterminate Western blot assay for anti–HIV-1 antibodies, with subsequent antibody seroconversion on follow-up; (2) a positive enzyme immunosassay (EIA) with Western blot confirmation within 12 months of a documented negative HIV-1 antibody result; or (3) an optical density signal-to-cutoff ratio of less than 0.75 according to a less sensitive and standard dual EIA testing system,15 provided there was a history compatible with recent HIV infection and a CD4 cell count higher than 200/µL.

Participants were excluded from the analysis of primary resistance if they had received antiretroviral therapy for more than 7 days before blood collection for resistance testing. The study was approved by the University of California, San Francisco, institutional review board, and written informed consent was obtained from all study participants.

**Genotypic Assessment**

Genotypic resistance is defined as the presence of viral mutations associated with impaired drug susceptibility or virologic response as specified by the International AIDS Society-USA mutations panel, with alterations as noted.16 The presence of at least 1 primary mutation (PR D30N, M46I, G48V, V82A, I84V, or L90M) was required for genotypic protease inhibitor (PI) resistance, while any mutation was used to define genotypic resistance to nucleoside reverse transcriptase inhibitors (NRTIs) (RT M41L, E44D, K65R, D67N, any insertion at T69, K70R, L74V, V75T, V118I, Q151M, M184I/V, L210W, T215Y/F, and K219Q) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) (RT A98G, L100I, K103N, V106A, V108I, Y181C/I, Y188C/L/H, and G190A). In addition, the RT T215C/D/S/N mutations were included because they indicate previous resistance involving the RT T215Y mutation.17 For 213 participants, the presence of mutations was assessed by population sequencing of codons 3 to 99 of the protease gene and codons 38 to 247 of the reverse transcriptase reading frame by using the TRUGENE HIV-1 Genotyping Kit (Visible Genetics, Inc, Atlanta, Ga). For 12 individuals with limited specimen, a noncommercial method of automated cycle sequencing of the protease and reverse transcriptase reading frames was used.18

Information from sequencing reactions was assembled with OpenGene software (Visible Genetics, Inc) or Seqman (DNASTAR, Madison, Wis) and proofread manually. Mixtures of sequences were reported if 2 or more bases had more than 20% relative peak

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**Figure 1. Genotypic and Phenotypic Resistance by Class of Antiretroviral Drugs by Calendar Year**

- 243 Eligible Patients With Recent HIV-1 Infection
- 18 Excluded (Resistance Genotype Unavailable)
- 225 Completed Resistance Genotype Within 7 Days of Initiation of Antiretroviral Therapy
- 34 Patients Did Not Receive Treatment
- 141 Patients Received Treatment
- 111 Had No Evidence of Resistance to Regimen Used
- 106 Were Parsensitive and Were Treated With PI + NRTI
  - 5 Had NRTI Resistance Alone and Were Treated With PI + NRTI
- 30 Had Evidence of Resistance to Regimen Used
  - 7 Had PI Resistance and Were Treated With PI + NRTI
  - 21 Had NRTI Resistance and Were Treated With PI + NRTI
  - 1 Had NRTI Resistance and Was Treated With 3 NRTIs
  - 1 Had NRTI Resistance and Was Treated With NNRTI

All treated individuals received 3 or more antiretroviral agents. PI indicates protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.

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**Table 1. Participant Characteristics by Time Interval***

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Participants, No.</td>
<td>12</td>
<td>28</td>
<td>53</td>
<td>41</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>10 (83.3)</td>
<td>24 (85.7)</td>
<td>50 (94.3)</td>
<td>37 (90.2)</td>
</tr>
<tr>
<td>Men who have sex with men, No. (%)</td>
<td>10 (83.3)</td>
<td>22 (78.6)</td>
<td>46 (86.8)</td>
<td>35 (85.4)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>34.8 (5.5)</td>
<td>34.2 (7.9)</td>
<td>35.4 (9.1)</td>
<td>35.5 (10.4)</td>
</tr>
<tr>
<td>Less sensitive optical density to cutoff ratio, median (IQR percentile)</td>
<td>0.51 (0.13-0.67)</td>
<td>0.04 (0.03-0.21)</td>
<td>0.16 (0.02-0.50)</td>
<td>0.26 (0.01-0.50)</td>
</tr>
<tr>
<td>Viral load, median (IQR percentile)</td>
<td>19505 (2175-34 603)</td>
<td>14 457 (1723-69 185)</td>
<td>30 000 (4572-127 142)</td>
<td>59 483 (12 467-259 009)</td>
</tr>
<tr>
<td>CD4 cells, median, No. (IQR percentile)</td>
<td>515 (394-965)</td>
<td>533 (375-658)</td>
<td>510 (403-602)</td>
<td>483 (356-577)</td>
</tr>
<tr>
<td>CD4 cells, % (of CD3 cells) (IQR percentile)</td>
<td>31 (22-41)</td>
<td>28 (23-37)</td>
<td>30 (24-36)</td>
<td>31 (22-35)</td>
</tr>
</tbody>
</table>

*IQR indicates interquartile range.
height in the forward and reverse sequencing reactions. Consensus sequences from different individuals were aligned and manually edited, and neighbor-joining phylogenetic trees were used to seek evidence of laboratory contamination.

**Phenotypic Assessment**

Phenotypic drug-susceptibility testing was performed with the Phenosense Assay (ViroLogic, Inc, South San Francisco, Calif). Viruses were defined as resistant if the fold change in IC$_{50}$ (inhibitory concentration, or the concentration of a drug that inhibits viral replication by 50%) was at least 1.7 for stavudine, didanosine, and zalcitabine; at least 4.5 for lamivudine, zidovudine, and abacavir; at least 10 for delavirdine, efavirenz, nevirapine, and lopinavir; and at least 4 for nelfinavir, amprenavir, saquinavir, indinavir, and ritonavir (N.S.H., written communication, January 2002). For abacavir, stavudine, didanosine, and lopinavir, the phenotypic cutoffs were levels of drug susceptibility above which there is detectable impairment in virologic response. For NNRTIs, the 10-fold cutoff represents the upper limit of the normal range of biological variation, below which virologic responses were normal in small clinical series. For other drugs, the phenotypic cutoffs were based on assay precision, biological variability, and limited clinical experience. Phenotypic resistance defined by using cutoffs of 2.5 and 10 are also reported to allow comparison with prior reports.

**Other Laboratory Assays**

Plasma viral RNA load was measured with the Roche HIV-1 Amplicor Monitor assay (Roche Diagnostics, Branchburg, NJ), and CD4 cell counts were measured by using flow cytometry.

**Statistical Analysis**

Before analysis, the data were categorized by year of enrollment for convenience and to allow correlation with other epidemiologic information. For statistical analysis and reporting of resistant proportions, the calendar-year periods were collapsed into 3 intervals, 1996 and 1997, 1998 and 1999, and 2000 and 2001, which allowed primary resistance proportions to be estimated with greater precision in 3 periods. Comparisons with categorical variables throughout the study were evaluated with the Fisher exact test. Differences in continuous variables were evaluated with Kruskal-Wallis tests. Time trends in the prevalence of drug resistance were assessed with the Cochran-Armitage exact trend test. To ensure that dividing observations into time periods did not bias the results, the proportion resistant was also evaluated with logistic regression by using study enrollment date to predict the probability of resistance. Multiple logistic regression was used to determine whether any genotypic evidence of drug resistance was associated with the duration of HIV infection and CD4 cell count and whether primary resistance changed over time after these baseline factors were controlled. Viral load data were available from weekly time points for the first 4 weeks and then monthly time points thereafter. Time to viral load suppression was evaluated with Kaplan-Meier survival analysis. All statistical tests were 2-tailed (P<.05). Data analyses were performed with SAS version 8.2 (SAS Institute, Cary, NC).

**RESULTS**

**Cohort Characteristics**

From June 10, 1996, through June 30, 2001, 243 participants were found to have evidence of recent HIV-1 infection (FIGURE 1). All of these participants were included in the study of primary drug resistance. Eighteen (7.4%) were excluded from the analysis because a drug-resistance genotype was unavailable from a point within 7 days of initiation of antiretroviral therapy. The reasons for an unavailable genotype included no specimen available (n=9) or a failed genotyping assay (n=9). The remaining 225 participants were divided according to the year they were identified. There were no significant differences over time in age, sex, risk group, CD4 cell count, CD4 percentage, or viral load (TABLE 1). The mean optical density to cutoff ratio in the less-sensitive EIA test fluctuated significantly in the first 2 years of the study but did not change significantly after 1997. Resistance determinations were obtained before any treatment in 215 (95.6%) participants and during the first 7 days of treatment in 10 (4.4%) persons. Genotypic analysis was based on the TRUGENE HIV-1 Genotyping Kit (Visible Genetics, Inc) in 213 persons (94.7%) and a noncommercial cycle sequencing assay in the remaining 12 (5.3%). The demographic characteristics of the overall sample were comparable to those of seroincident cases of HIV-1 in San Francisco as defined by an expert consensus panel in 1997.

**Genotypic Analysis**

Genotypic evidence of resistance was detected in 52 (23.1%) individuals (TABLE 2). The proportion with genotypic resistance to NRTIs varied significantly over time, decreasing from 25.0% (10/40) in 1996-1997 to 7.4% (7/
94) in 1998-1999 and then increasing to 20.9% (19/91) in 2000-2001 (test for homogeneity, \( P = .007 \)). The prevalence of genotypic resistance to PIs was 2.5% in 1996-1997 and 7.7% in 2000-2001 (trend test, \( P = .25 \)). Genotypic resistance to NNRTIs increased steadily from 0% in 1996-1997 to 13.2% in 2000-2001 (trend test, \( P = .01 \)). Genotypic resistance to 2 or more classes of antiretroviral drugs increased from 2.5% (1/40) in 1996-1997 to 13.2% (12/91) in 2000-2001 (trend test, \( P = .004 \)). Only 1 (0.4%) of 225 recently infected individuals had genotypic resistance to all 3 classes of antiretroviral therapy. Plots of time trends by calendar year suggest rapid and recent increases in primary resistance to NNRTIs, while resistance to PIs appeared earlier and has remained more stable (FIGURE 2).

Phenotypic Analysis

Phenotypic drug susceptibility testing was attempted in all 225 participants with completed genotypic analysis and was successful in 210 (93.3%) (TABLE 3). The proportion of new in-
Table 3. Summary of Phenotypic Susceptibility Over Time*

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Susceptibility</th>
<th>1996-1997 (n = 38)</th>
<th>1998-1999 (n = 91)</th>
<th>2000-2001 (n = 81)</th>
<th>Trend†</th>
<th>Homogeneity‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitor (NRTI)</td>
<td>Any NRTI resistance defined by using clinical cutoffs (1.7- to 4.5-fold)</td>
<td>8 (21.0)</td>
<td>3 (3.3)</td>
<td>5 (6.2)</td>
<td>.03</td>
<td>.004</td>
</tr>
<tr>
<td></td>
<td>&gt;2.5-fold increase in IC&lt;sub&gt;50&lt;/sub&gt; to any RTI</td>
<td>5 (13.1)</td>
<td>4 (4.4)</td>
<td>6 (7.4)</td>
<td>.46</td>
<td>.21</td>
</tr>
<tr>
<td></td>
<td>&gt;10-fold increase in IC&lt;sub&gt;50&lt;/sub&gt; to any RTI</td>
<td>3 (7.9)</td>
<td>0</td>
<td>4 (4.9)</td>
<td>&gt;.99</td>
<td>.02</td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitor (NNRTI)</td>
<td>Any NNRTI resistance defined by using clinical cutoffs (10-fold)</td>
<td>0</td>
<td>4 (4.4)</td>
<td>8 (9.9)</td>
<td>.02</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>&gt;2.5-fold increase in IC&lt;sub&gt;50&lt;/sub&gt; to any NNRTI</td>
<td>9 (23.7)</td>
<td>21 (23.1)</td>
<td>22 (27.2)</td>
<td>.66</td>
<td>.83</td>
</tr>
<tr>
<td>Protease inhibitor (PI)</td>
<td>Any PI resistance defined by using clinical cutoffs (4-fold)</td>
<td>1 (2.6)</td>
<td>2 (2.2)</td>
<td>5 (6.2)</td>
<td>.32</td>
<td>.45</td>
</tr>
<tr>
<td></td>
<td>&gt;2.5-fold increase in IC&lt;sub&gt;50&lt;/sub&gt; to any PI</td>
<td>4 (10.5)</td>
<td>8 (8.8)</td>
<td>13 (16.0)</td>
<td>.31</td>
<td>.33</td>
</tr>
<tr>
<td></td>
<td>&gt;10-fold increase in IC&lt;sub&gt;50&lt;/sub&gt; to any PI</td>
<td>1 (2.6)</td>
<td>0</td>
<td>5 (6.2)</td>
<td>.16</td>
<td>.03</td>
</tr>
<tr>
<td>Any</td>
<td>Clinical resistance to ≥1 drug class</td>
<td>8 (21.0)</td>
<td>9 (9.9)</td>
<td>13 (16.0)</td>
<td>.79</td>
<td>.21</td>
</tr>
<tr>
<td>Any</td>
<td>Clinical resistance to ≥2 drug classes</td>
<td>1 (2.6)</td>
<td>0</td>
<td>4 (4.9)</td>
<td>.35</td>
<td>.10</td>
</tr>
<tr>
<td>All</td>
<td>Clinical resistance to all 3 drug classes</td>
<td>0</td>
<td>0</td>
<td>1 (1.2)</td>
<td>.57</td>
<td>.57</td>
</tr>
</tbody>
</table>

*IC<sub>50</sub> indicates the inhibitory concentration, or the concentration of the drug that inhibits viral replication by 50%.
†Two-sided P value from Cochran-Armitage exact trend test.
‡Two-sided P value from Fisher exact test.

Virologic Responses to PI-Containing Therapy

To determine whether primary resistance was associated with delayed virologic response, we analyzed the time to virologic suppression, defined as the first plasma viral RNA concentration less than 500 copies/mL. This analysis included only the subset of 141 (62.7%) participants who initiated antiretroviral therapy, which consisted of NRTIs and a PI in 139 participants, NRTIs and an NNRTI in 1 individual, and 3 NRTIs in 1 individual (Figure 2). Participants were classified according to whether there was genotypic resistance to any antiretroviral drug class used. If therapy was stopped for any reason, observations were excluded from the analysis after the last treatment date. Resistance testing was not used to select the initial drug regimen in any participant. Median time to viral load suppression was longer in 30 participants with genotypic resistance compared with 111 without resistance (Figure 3, 12 weeks vs 5 weeks; log-rank test, P = .02). One of these individuals was infected with HIV-1 resistant to NRTIs and PIs and had persistent plasma viral load after 6 months of combination therapy, as reported earlier.4

Baseline Correlates of Genotypic Drug Resistance

The detection of primary genotypic resistance was more frequent among individuals who were infected for shorter periods, as estimated by the less-sensitive EIA optical density to cutoff ratio (Spearman rank correlation, P = .02). The detection of genotypic resistance was 28.8% among those in the first quartile of duration of infection, 27.4% among the second quartile, 19.2% among the third quartile, and 9.9% among the fourth quartile.
The proportion of recent infections that involve NNRTI resistance increased rapidly in this serial cross-sectional survey. Treatment with NNRTIs became more common in late 1998, when clinical trial results indicated that virologic outcomes during treatment with an NNRTI were comparable with those of PI-based treatment. Increases in primary NNRTI resistance observed after 1999 in this study likely reflect more prevalent use of NNRTIs in the previous year. A study of primary drug resistance in the United Kingdom also reported trends toward increasing primary genotypic resistance, which included NNRTI resistance in 3 of 26 (11.5%) individuals in 2000 and none of 22 individuals in 1997 through 1999. Similarly, cases of primary PI resistance appeared in San Francisco and Geneva after approximately 1 year of widespread PI exposure.

In contrast to primary NNRTI resistance, primary PI resistance remained relatively stable from 1997 through 2001 (Figure 2). The transmission of HIV-1 resistance to all 3 available classes of antiretroviral therapy continues to be rare, occurring in only 1 of 225 (0.4%) individuals in this series. In contrast, the prevalence of 3-class drug resistance among 268 drug-experienced participants presenting for clinical resistance testing in our laboratory in San Francisco was 14.3% during 2000-2001 (data not shown). The frequent transmission of 3-class multidrug resistance in our series from San Francisco and elsewhere may reflect the poor replication capacity of these extensively mutated viruses. Just as lower viral load in untreated individuals was associated with decreased sexual transmission, so too the lower viral load typically observed during multidrug resistant viremia may diminish the frequency of transmission of these viruses. In contrast, NNRTI-resistant viruses demonstrate relatively high levels of plasma viral load during drug failure and may prove to have concordantly preserved capacity for transmission.

The changing proportions of NRTI-resistant HIV-1 over time may reflect changing virologic outcomes among persons who transmit HIV-1. Before 1996, antiretroviral therapy consisted of single or dual NRTIs, which typically lead to viremia with drug-resistant HIV-1 in the majority of patients. Transmission of NRTI-resistant viruses in San Francisco may have decreased in 1998-1999 as treated populations changed to more active regimens that contain PIs, NRTIs, or both. Trends toward decreasing primary resistance to nucleoside analogues have been observed in other settings as well. Since 1998, genotypic resistance testing has indicated that the proportion of NRTI-resistant cases is increasing once again, although this trend was not confirmed by phenotypic analysis. Increases of genotypic resistance have possibly reflect restored infectiousness of extensively antiretroviral-experienced individuals. Alternatively, the observed changes in primary resistance prevalence could reflect changes in risk behavior, which were not assessed in this study. Further, although demographic characteristics did not change throughout the course of this study, changes in referral patterns may have occurred and contributed to the observed trends in resistance prevalence.

Drug-resistance testing is recommended for persons failing antiretroviral therapy and for HIV-1-infected pregnant women. For persons with primary HIV infection, the International AIDS Society-USA and Department of Health and Human Services guidelines indicate that resistance testing should be considered, and the EuroGuidelines group recommends testing. Our data support the use of resistance testing in recently infected persons in settings where antiretroviral use is widespread. In this sample of recently infected individuals, primary among the third quartile, and 11.5% among the quartile infected for the longest period. These indexes of the duration of infection were not associated with year of enrollment (Spearman rank correlation, P = .64). The initial plasma viral RNA load was highly variable, most likely because of rapid changes in viremia that occur during recent HIV-1 infection (Figure 4). There was no difference in initial plasma viral load between the individuals with resistant virus and those with sensitive virus (P = .71). In contrast, baseline CD4 cell counts and CD4 cell percentages were significantly higher among individuals infected with resistant HIV-1 (P = .02 and P = .04, respectively). Multivariate logistic regression indicated that a higher CD4 cell count was independently associated with resistant HIV-1 (P = .03) after duration of infection was controlled.
TWO PRIMARY PREVENTIVE STRATEGIES ARE WORTH CONSIDERING. One is to identify those infected with drug-resistant HIV-1 who have diminution of viral replication capacity. Whether primary resistance will worsen long-term virologic and clinical outcomes requires further study. Nevertheless, the growing prevalence of primary NNRTI resistance and the substantial prevalence of primary PI and NRTI resistance suggest that resistance testing has a role in guiding antiretroviral use in recently infected persons.

Overall, the prevalence of primary phenotypic resistance was less than the prevalence of genotypic resistance, partly because genotypes that indicate prior drug resistance but do not affect current susceptibility, such as the RT T215C/D/S/N mutation, were included. In addition, the genotyping assay detected some mixtures of resistant and sensitive HIV-1 that had normal susceptibility. Finally, the susceptibility cutoff values used to define phenotypic resistance have not been defined for all drugs, and conservatively high levels were selected when there was uncertainty.

The higher average CD4 cell count among individuals infected with drug-resistant HIV-1 suggests that resistant isolates may cause less initial injury to the immune system, possibly because of decreased viral replication capacity or decreased tropism for tissues involved in T-cell production, such as the thymus. Relatively preserved CD4 cell counts and slower T-cell turnover have been observed in individuals during multidrug-resistant viremia. Partially preserved CD4 cell counts and slower T-cell turnover have been observed in individuals during multidrug-resistant viremia. These partial CD4 cell-count responses require continued use of antiretroviral therapy, which maintains partial virologic load suppression and selection for drug-resistant HIV-1 that has diminished replication capacity. Our observations indicate that drug-resistant HIV-1 infection is associated with higher CD4 cell counts in drug-naive persons as well, providing additional evidence that CD4 cell-count sparing may be due to viral factors such as diminished replication capacity.

Primary HIV-1 drug resistance indicates that the risks of antiretroviral therapy extend beyond the treated individual to uninfected populations. Indeed, primary resistance indicates triple failure of the health care system, including failure of drug treatment to control viral replication in the source partner, failure of behavioral prevention in the source partner receiving treatment, and failure of behavioral prevention in the recently infected person. Intervention to minimize transmission of drug-resistant HIV-1 will require physician education to improve prescribing, more tolerable drug regimens, counseling to promote adherence, and more effective prevention programs targeted to infected and uninfected persons. Prevention programs specifically linked to treatment may serve to ensure that the clinical and epidemiological benefits of widespread antiretroviral therapy are not offset by increases in risk behavior and the transmission of drug-resistant HIV-1.

Author Contributions: Study concept and design: Grant, Hecht, Kahn. Acquisition of data: Grant, Hecht, Warmerdam, Liegler, Petropoulos, Chesney, Busch, Kahn. Analysis and interpretation of data: Grant, Hecht, Warmerdam, Liu, Hellmann, Kahn. Drafting of the manuscript: Grant, Hecht, Petropoulos, Kahn. Critical revision of the manuscript for important intellectual content: Grant, Hecht, Warmerdam, Liu, Hellinger, Chesney, Busch, Kahn. Statistical expertise: Grant, Hecht, Liu. Obtained funding: Grant, Hecht, Chesney, Busch, Kahn. Administrative, technical, or material support: Grant, Hecht, Warmerdam, Liegler, Hellmann, Chesney, Busch. Study supervision: Grant, Hecht, Liegler, Petropoulos.

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