Understanding Viral Suppression

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Disclosure

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  - GlaxoSmithKline
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Diversity of RNA Virus Populations

- Virus populations comprise a *quasispecies*
- Genetically distinct variants evolve from an initial oligoclonal inoculum
- Variants are generated by error-prone RNA-dependent polymerases
Drug-Resistant Mutants Preexist in Untreated Patients

- The HIV genome contains $10^4$ nucleotides.
- The mutation rate of HIV is $\sim 3 \times 10^{-5}$ nucleotides/replication cycle.
- $\sim 10^{10}$ virions are generated by $10^7 - 10^8$ rounds of replication each day.
Implications of viral dynamics for ART

- Inadequate HIV suppression will select rapidly for drug resistance mutations

- Accumulation of mutations leads to broader cross-resistance within a class

- Therefore, complete suppression of viral replication is essential for durable ART benefit
Key treatment goals

- Maximally and durably suppress plasma HIV RNA
- Restore and preserve immunologic function
- Reduce HIV-associated morbidity and prolong the duration and quality of survival
- Prevent HIV transmission

Defining virologic response to ART

- **Virologic suppression**
  - Confirmed HIV RNA level below the assay limit of detection

- **Virologic failure**
  - Inability to achieve or maintain suppression of viral replication to an HIV RNA level < 200 copies/mL

- **Incomplete virologic response**
  - Two plasma HIV RNA levels ≥ 200 copies/mL after 24 weeks on ART in a patient who has not yet achieved suppression

- **Virologic rebound**
  - Confirmed HIV RNA ≥ 200 copies/mL after virologic suppression

- **Virologic blip**
  - After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression

Real-time PCR quantification of VL

- Improved sensitivity
- Decreased variability
- Increased dynamic range
  - 20 to 10,000,000 copies/mL
- Automated sample processing
- New standardization and reporting
  - Copies/mL
  - <20 copies/mL
  - “Target not detected”
Low-level vireimia

● **Persistent low-level viremia:**
  – Confirmed detectable HIV RNA levels that are <1,000 copies/mL.

● **Virologic blip:**
  – After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

Causes of low-level viremia

- Persistent virus replication
- Persistent virus release from long-lived productively infected cells
- Episodic virus production from activated latently infected cells
- Non-adherence?
Detectable viremia by Taqman in patients with previously undetectable viremia

Persistent low-level viremia

- Persistent low-level viremia (PLLV, vRNA 50-1000 c/mL) is associated with increased risks of overt virologic failure\(^1,2\) immune activation\(^2\) and perhaps mortality\(^3\).
- Major drug resistance mutations are common in patients with vRNA < 1,000 c/mL (12.7% of 7861 samples from predominantly treatment-experienced patients)\(^3\). Less is known in the context of first-line antiretroviral therapy.
- Detection and management of drug resistance during PLLV remains a clinical challenge since conventional genotyping is validated for vRNA > 1,000 copies/mL.

3. Hull M et al. CROI 2010, Abstract 504
HIV-1 Drug Resistance Evolution During Persistent Low-Level Viremia

Babafemi Taiwo, Sébastien Gallien, Evgenia Aga, Heather Ribaudo, Richard Haubrich, Daniel Kuritzkes and Joseph Eron
Study Design

- Subjects were identified retrospectively from two ACTG clinical trials (A5142 and EFV arms of A5095)
- Cases with persistent low-level viremia (PLLV) were defined as subjects with HIV-1 RNA levels between 50 and 1000 c/mL on at least 2 occasions during a 6-month period or longer while on randomized ART
  - One HIV-1 RNA <50 or >1000 c/mL within a 6-month period was allowed
- Plasma virus during PLLV was sequenced
- Pre-treatment reverse transcriptase (RT) and protease (PR) sequences were obtained from the parent study
  - Stored plasma was sequenced if these were not available
Resistance data

- Sequence data obtained in samples from 54 of 65 (83%) patients.
- New resistance mutations detected in samples from 20 of 54 participants (37%)
- Most common mutations included:
  - 184I/V (14)
  - 103N (9)
  - 230L (3)

Taiwo B et al J Infect Dis 2011
# Distribution of maximum VL among subjects with and without resistance

<table>
<thead>
<tr>
<th></th>
<th>New Resistance</th>
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<tbody>
<tr>
<td></td>
<td>No (N=31)</td>
</tr>
<tr>
<td><strong>Maximum VL during PLLV</strong></td>
<td></td>
</tr>
<tr>
<td>50-100 c/mL</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>100-200 c/mL</td>
<td>8 (62%)</td>
</tr>
<tr>
<td>&gt;200 c/mL</td>
<td>16 (52%)</td>
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Taiwo B et al J Infect Dis 2011
Conclusions

- PLLV was observed in 5% of our trial population.
- Accumulation of resistance during PLLV occurred in 37% of evaluable cases (most commonly to 3TC and EFV).
- Accumulation of resistance more common in patients with VL>200 c/mL.
  - But, 38% with VL 100-200 c/mL had resistance.
- Most patients with resistance resuppressed (65% vs 74% with WT), but confirmed VL>1000 more common in patients with resistance (30% vs 9%, p=0.05).

Taiwo B et al J Infect Dis 2011
Plasma virus load in patients with and without virologic failure
Emerging Integrase Inhibitor Resistance Mutations in Raltegravir-Treated HIV-1-Infected Patients with Low-Level Viremia

Sébastien Gallien, Constance Delaugerre, Isabelle Charreau, Joséphine Braun, Thomas Boulet, Aurélie Barrail-Tran, Nathalie De Castro, Jean-Michel Molina and Daniel R. Kuritzkes
ANRS 138 “Easier” Trial

**Inclusion criteria:**
- Highly treatment-experienced HIV-1 infected pts
- With a 3 months unchanged optimized background regimen (OBR) + enfuvirtide (ENF)
- Plasma HIV-1 RNA levels <400 cp/mL
Results

- 49 patients experienced 94 episodes of LLV while receiving RAL
  - Median VL 100 c/mL (IQR, 75-167 c/mL)
- Genotyping successful in 73 samples (78%) from 39 patients (80%)
- Significant INSTI resistance mutations detected in 3 (7.7%, 95% CI 1.6%-20.9%)
  - N155H (2)
  - P145S (1)

Gallien S et al AIDS 2011
Plasma HIV-1 RNA levels in patients developing INSTI resistance mutations
Conclusions

- Low-level viremia in patients receiving RAL in the ANRS 138-EASIER trial was detected in 29% during their 48-week follow-up.
- INSTI resistance mutations emerged in 7.7% of these patients.
  - No factors predictive of INSTI resistance were identified
- The development of INSTI resistance at VL <1000 c/mL emphasizes the importance of documenting resistance and considering a change in ART at low levels of viremia.

Gallien S et al AIDS 2011
Prevalence and Significance of HIV-1 Drug Resistance Mutations among Patients on Antiretroviral Therapy with Detectable Low-Level Viremia

Jonathan Z. Li, Sébastien Gallien, Tri D. Do, Jeffrey N. Martin, Steven Deeks, Daniel R. Kuritzkes and Hiroyu Hatano
Methods

- **Study and Subject Selection**
  - SCOPE cohort participants with a viral load <1,000 copies/mL on 3-drug ART and available plasma

- **Sample Processing and Sequencing**
  - Plasma ultracentrifuged prior to RNA extraction
  - Coding regions of HIV-1 PR, RT, IN, and gp41 amplified by nested gene-specific primers

- **Data and Statistical Analysis**
  - Fully active ARV defined as having a Stanford resistance mutation score <10
  - Medication adherence (30 days) by self-report
  - Repeated measures multivariable logistic regression used to evaluate predictors of resistance accumulation

Li J et al Antimicrob Agents Chemother 2012
Results

- **Baseline Characteristics**
  - Genotyping successful at 82 time points between 2001-2010 for 47 participants
  - Median VL of the LLV episodes was 267 copies/mL
  - There was no significant association between VL and number of fully active ARVs (P=0.69)

- **Evolving HIV Resistance**
  - Compared to a prior genotyping, 46% (18/39) of LLV samples had a new resistance mutation
  - In those with ≥2 LLV episodes, 44% (8/18) accumulated new resistance over a median 11 months
  - On multivariable analysis, fewer fully active ARVs at the prior time point (P=0.003) and longer elapsed time (P=0.02) were associated with the rise of new resistance controlling for adherence and VL

Li J et al Antimicrob Agents Chemother 2012
**Conclusions**

- New drug resistance mutations were frequently detected during LLV episodes compared to prior genotyping.

- Early resistance genotyping or regimen switches may prevent the accumulation of resistance mutations.

- The majority of LLV episodes were followed by virologic suppression.

Increased Risk of Virologic Rebound in Patients on Antiviral Therapy with Isolated Detectable Viral Loads <48 Copies/mL by Taqman RT-PCR Assay

Timothy J. Henrich, Brian R. Wood, Daniel R. Kuritzkes
Methods

- Retrospective electronic medical/laboratory record study
  - 778 HIV patients on ART
- Cox proportional hazard regression modeling to investigate the effects of the 1st HIV-1 load measurement after introduction of Taqman RT-PCR assay (time-point T0) on risk of a confirmed or last VL >50, >200, >400 and >1,000 copies/mL
- Final censoring at 22 months follow-up
- Cox regression was repeated using a 1:2 propensity score BLQ-matched TND comparator cohort to reduce potential differences between baseline comparator cohorts (TND & BLQ)
- Propensity scores calculated by the nearest neighbor method including all study covariates

Adjusted Cumulative Hazard of Virologic Failure by T0 Viral Load Group

Clinical outcome after rebound

- **53/778 (6.8%)** patients experienced viral rebound >200
  - 30% underwent a change in ART
  - 55% re-suppressed to <50 copies/mL
  - of 24/53 that did not re-suppress <50:
    - 42% had persistent VL >200
    - 21% had persistent LLVL >50 but <200
    - 37% had no further VL info available

- **Routine resistance testing attempted on 34 patients**
  - interpretable results in 22 cases,
  - 9 with drug resistance (6 to NNRTI)
  - all patients with resistance changed ART regimen
  - 7 of 9 patients with resistance re-suppressed after ART change

Summary and Conclusions

- VLLV is associated with greater risk of viral rebound at >50, >200, and >400 copies/mL (but not with >1,000 copies/mL)
- Lower CD4 & younger age associated with greater risk of rebound at all levels
- Majority of patients with rebound >200 re-suppressed
- Very few patients experienced rebound >1000 copies/mL
- Development of resistance was rare
- Lowering the VL used to define “full suppression” in our population could result in needless switching to 2nd- and 3rd-line regimens and increased cost

Summary and Clinical Recommendations

- **Low-level viremia (<1000 c/mL)**
  - No change needed for VL < 48
  - No consensus on management for VL 48-200 c/mL
    - Follow closely
  - Consider VL 200-1000 c/mL as possible virologic failure
    - Attempt resistance testing if VL > 500 c/mL

- **Repeated detectable viremia (>1000 c/mL) without detectable resistance**
  - Consider resuming same regimen, repeat resistance test if failure to suppress