Virologic Failure Following Persistent Low-level Viremia in a Cohort of HIV-Positive Patients: Results From 12 Years of Observation

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Background:

- Suppression of HIV viral load improves survival and decreases risk of development of resistance to ART
- Current goal: virologic suppression below limit of assay detection (<20-75 copies/ml)
- However, low-level viremia (< 1000 copies/ml, LLV) not infrequently encountered
- Blips <400 copies/ml are common and do not reflect viral replication or predict failure
- US DHHS Guidelines:
  - virologic failure = persistent viral load > 200 copies/ml (associated with resistance mutations)
  - No consensus about management of patients with VL of 50-200 copies/ml
- **Study objective**: to assess the impact of persistent low-level viremia (LLV) on the subsequent risk of virologic failure (>1000 copies/ml)

Methods:

- HIV cohort from Montreal, Canada, consisting of 2416 HIV positive patients, recruited from 1997 onwards and with data collected every 3 months
- 1999-2010: Versant HIV-1 RNA 3.0 Assay (LLD <50 copies/ml)
- Since 2010: Abbot Real-Time HIV-1 assay (LLD <40 copies/ml)
- Inclusion criteria:
  - ART for $\geq$12 months; VL <1000 copies/ml
  - for analysis of persistence of LLV: undetectable VL or LLV; at least 2 VL measurements after persistence period
- **Primary outcome**: cumulative incidence of virologic failure (> 1000 copies/ml) according to 4 different groups: 1) undetectable VL, 2) persistent LLV of 50-199 copies/ml, 3) persistent LLV of 200-499 copies/ml and 4) persistent LLV of 500-999 copies/ml
- Duration of persistence was analyzed for duration of LLV of $\geq$ 6, $\geq$ 9 and $\geq$ 12 months
- Follow-up until virologic failure or last most recent VL measurement
- Statistics:
  - Kaplan-Meier survival analysis with log-rank test
  - 3-year cumulative incidence of virologic failure (6 months persistence status) stratified according to period of LLV
  - Cox proportional hazard regression models for multivariate analysis

Results:

- Table 1: 1860 patients, 94% male, 92% white, 86% homosexual, median follow-up 7.1
- ART: Lopinavir (17%), Efavirenz (27%), NRTI-only regimen in 13%
- **Figure 1:** Cumulative incidence of virologic failure over 5 years
  - Persistent LLV of 50-199 copies/ml was associated with higher risk of virologic failure compared to undetectable VL regardless of duration of persistence

- **Table 2**: incidence of virologic failure for persistence duration ≥ 6 months
    - <50: **5** per person-year of follow-up
    - 50-199: **14**; 56% achieved <50 copies/ml before LLV, and 34% had episode of <50 copies/ml between LLV and virologic failure
    - 500-999: **29**
- **Figure 2**: 3-year cumulative incidence of virologic failure according to periods when LLV occurred (6-month persistence)
    - Lowest risk of virologic failure with <50 copies/ml regardless of the period
    - ? trend toward decreasing risk with 50-199 copies/ml recently
- **Table 3:** multivariate analysis for risk of virologic failure
    - Hazard ratio 2.2 for persistent LLV 50-199 and 200-499 copies/ml
    - Hazard ratio 5 for 500-999 copies/ml
    - "significant" confounding variables: date of HIV infection, use of certain antiretroviral drugs
- ?Protective effect of certain ART drugs (abacavir, tenofovir, efavirenz, ritonavir)

Discussion:

- LLV of ≥ 6-12 months is associated with an increased incidence of and risk for virologic failure, even if only 50-199 copies/ml.
- Study powered to show significant relative risks in all models
- Strengths: first study to investigate 3 categories of LLV and 3 persistence periods; long follow-up
- Most previous studies only examined LLV of 50-500 copies/ml and used >500 as definition of virologic failure; HR of 2-5 similar to the present study.
- Limitations:
    - White homosexual men
    - Too small to consider different effect of ART regimens
    - LLV rare event, hence wide confidence intervals and limitations in number of possible confounders for adjustment
    - No data re ART regimen changes, adherence, drug interaction issues
    - No data about resistance mutations following LLV
    - No data about initial resistance mutations and pretreatment VL
- Conclusion: persistent LLV ≥ 6 months increases risk of subsequent virologic failure

Clinical consequences of LLV of 50-199 copies/ml ?

- Adherence counseling
- Measurement of plasma ART levels; check for drug interactions
- Change of regimen (blindly vs. genotyping) vs. observation for 6-12 months?

Genotyping if VL >500 or ideally> 1000
Unlike the case with higher levels of HIV RNA, most, if not all, circulating virus from individuals with this level of HIV RNA results from the release of HIV from long-lived latently infected cells and does not signify ongoing viral replication with the emergence of drug-resistant virus

Patients with persistent HIV RNA levels >200 copies/mL often select out drugresistant viral variants, particularly when HIV RNA levels are >500 copies/mL. Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should be considered as possible virologic failure; resistance testing should be attempted if the HIV RNA level is >500 copies/mL. For individuals with sufficient therapeutic options, consider treatment change

- Blips <400 copies/ml are common and do not reflect viral replication or predict failure (isolated rebound after suppression)

Statistik: multivariate Analyse, confounder wurden im Model behalten, wenn sie die Hazard ratio um mindestens plus/minus 10% verändert haben