How do you measure HIV cure

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Background

Active ongoing HIV replication

Antiretroviral drugs suppress HIV replication

Circulating virus

Limit of detection

Time

D Smith, MD, at Los Angeles, CA: April 25, 2016, IAS-USA
Antiretroviral drugs suppress HIV replication

Background

Active ongoing HIV replication

Antiretroviral drugs suppress HIV replication

HIV rebounds

Potent antiretroviral compounds can NOT cure HIV infection

Antiviral compounds CAN cure HCV infection
Antiretroviral drugs suppress HIV replication. HIV rebounds from viral reservoir.

Background:

Active ongoing HIV replication
Establishment of viral reservoir

Antiretroviral drugs suppress HIV replication

HIV rebounds
HIV rebounds from viral reservoir
Major hurdle towards HIV cure

- HIV reservoir of latently infected cells
- How is the viral reservoir been formed
Measure of HIV Cure = Measure the viral reservoir

Infection → Latently infected [zzzz] → Reactivation

How much HIV DNA can we detect inside the latent cells

How many cells can reactivate infectious virus
What do we know about the viral reservoir?

Measure the viral reservoir: HIV reactivation

Quantitative viral outgrowth assay (QVOA): infectious virus
Measure the viral reservoir: HIV reactivation

Quantitative viral outgrowth assay (QVOA): infectious virus
Measure the viral reservoir: HIV reactivation

Quantitative viral outgrowth assay (QVOA): infectious virus
Measure the viral reservoir: HIV reactivation

Mouse viral outgrowth assay (MVOA): infectious virus
Measure the viral reservoir: HIV reactivation

Mouse viral outgrowth assay (MVOA): infectious virus

Humanized immune system

50 million cells

Metcalf Pate et al, JID, 2015
Measure the viral reservoir: HIV DNA

• Development of ultra-sensitive techniques (LTR-IN)
• Detect large majority of HIV subtypes and CRFs > 95% infections worldwide HIV-1 subtypes

Bosman et al, JIAS, 2018
Measure the viral reservoir: HIV DNA

Besson et al, CID, 2014; Bosman et al, manuscript in preparation, Poster AIDS2018, WEPEA030
Apply measure of HIV reservoir in a Cure strategy

Berlin Patient: HIV infected, on ARVs and diagnosed with AML

Transplantation with stem cells from a donor lacking the CCR5 receptor for virus entry into the cell

ARVs were stopped at transplantation

No sign of HIV replication afterwards (>10 years)

Hutter et al, NEJM, 2008
HIV Cure: stem cell transplantation: IciStem

International collaboration to guide and investigate the potential for HIV cure in HIV-infected patients requiring allogeneic stem cell transplantation for hematological disorders
HIV Cure: stem cell transplantation: IciStem

- 37 patients registered from 9 different countries
- 30 patients transplanted
- All patients are on ARVs
- Mean follow-up: 887 days
  - 12 patients beyond 2nd year post-SCT

<table>
<thead>
<tr>
<th>CCR5WT/WT</th>
<th>CCR5Δ32/Δ32</th>
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<tr>
<td>Adult Donor</td>
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<tr>
<td>alive</td>
<td>13</td>
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</tbody>
</table>
HIV Cure: stem cell transplantation: IciStem

Ultra-sensitive HIV DNA quantification in total PBMC DNA

Besson et al, CID, 2014
HIV Cure: stem cell transplantation: IciStem

IciS-19
CCR5d32 GvHD

IciS-03
CCR5WT GvHD

Measure of HIV reservoir = Measure of HIV cure

HIV RNA (c/ml plasma) undetectable

Total HIV DNA (c/10^6 cells) undetectable

QVOA (IUPM) undetectable undetectable

MVOA undetectable undetectable

Salgado et al, Annals of Internal Medicine, 2018
Measure of viral reservoir

Autopsy studies (FIND study in SA)

HIV Cure: stem cell transplantation: IciStem

NO HIV detected in CSF, gut and LN

Measure of HIV reservoir = Measure of HIV Cure

Analytical treatment interruption

Salgado et al, Annals of Internal Medicine, 2018
Concluding remarks

• We have very sensitive techniques to measure the viral reservoir
• We can not measure the viral reservoir in the whole body

• Measure of HIV reservoir ≠ Measure of HIV cure

• A specific biomarker to identify the reservoir
  – Quantify and characterize the reservoir
  – Can be used in total body PET scan
  – Can be used in specific HIV targeting and elimination
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