Maximizing Potency: Integrase Inhibitors and Adherence Challenges

Suzanne McCluskey, MD

Adherence 2019 • June 17-19 • Miami
Disclosures

• I have received research grants from:
  – The National Institute of Allergy and Infectious Diseases
  – MGH ECOR Fund for Medical Discovery
  – Harvard University CFAR
  – Gilead Sciences Research Scholars Program in HIV
  – ViiV Healthcare (Investigator-sponsored research)

• I have no conflicts
Outline

• A new era for global ART
• Introduction to integrase inhibitors
• Is dolutegravir (DTG) resistance-proof?
• Potential barriers to adherence to DTG
• Key questions for the research community
• A new era for global ART
• Introduction to integrase inhibitors
• Is dolutegravir (DTG) resistance-proof?
• Potential barriers to adherence to DTG
• Key questions for the research community
Why now?
Why now?

Why integrase inhibitors?
Rising Pretreatment NNRTI Resistance

World Health Organization Response

Pretreatment NNRTI Resistance
>10%

Urgently consider non-NNRTI based ART for all starters

Landmark Global Pricing Agreement

UNAIDS

21 September 2017

Price reduction of the dolutegravir-based antiretroviral therapy regimen

A New Generic Regimen: TLD

- Fixed dose combination
  - Tenofovir disoproxil fumarate
  - Lamivudine
  - Dolutegravir
- $75 per person/year
  - 10-15% less than EFV-based ART
Groups to receive TLD

• First-line ART
  – ART-naïve patients
  – Patients currently on NNRTI-based regimens
    • Most guidelines require viral suppression within the past 6 months

• Second-line ART
  – More variability in national guidelines
Scale of TLD Implementation

https://apps.who.int/iris/bitstream/handle/10665/275468/WHO-CDS-HIV-18.21-eng.pdf?ua=1
Outline

• A new era for global ART
• **Introduction to integrase inhibitors**
• Is dolutegravir (DTG) resistance-proof?
• Potential barriers to adherence to DTG
• Key questions for the research community
Integrase inhibitors

Integrase inhibitors

Genetic Barrier to Resistance

- Number of mutations needed for resistance
- Frequency of mutation development
Genetic Barrier to Resistance

Number of mutations needed for resistance
Frequency of mutation development

We want to choose a drug with a high genetic barrier
Evolution of Integrase Inhibitors

Early Generation

Late Generation

Higher resistance barrier

Evolution of Integrase Inhibitors

Early Generation

Late Generation

Catalytic triad

Higher resistance barrier

Benefits of DTG vs NNRTIs

• Higher barrier to resistance

Benefits of DTG vs NNRTIs

• Faster rates of viral suppression

Median time to suppression:
• DTG arm: 28 d
• EFV arm: 84 d

Benefits of DTG vs NNRTIs

• Better tolerability
• Drug discontinuation due to side effects in SINGLE:
  – DTG arm: 2% (10 out of 414 participants)
  – EFV arm: 10% (42 out of 419 participants)
Does adherence still matter?
Does adherence still matter?

YES!
Does adherence still matter?

- 80-90% of those failing NNRTI-based ART have resistance

- Now with a high barrier to resistance drug, the great majority of failures will be due to poor adherence
Outline

• A new era for global ART
• Introduction to integrase inhibitors
• Is dolutegravir (DTG) resistance-proof?
• Potential barriers to adherence to DTG
• Key questions for the research community
Clinical Trials of ART Naïve Subjects

% suppressed to <50 copies/mL at 48 weeks

Clinical Trials of ART Naïve Subjects

0 out of 1627 clinical trial participants failed with resistance to DTG

Only a matter of time
Only a matter of time

• Reported resistance to DTG in ART-naïve persons
  – Cohort data
  – Case reports
Groups to receive TLD

• First-line ART
  – ART-naïve patients
  – Patients currently on NNRTI-based regimens
    • Most guidelines require viral suppression within the past 6 months
Groups to receive TLD

• First-line ART
  – ART-naïve patients
  – Patients currently on NNRTI-based regimens
    • Most guidelines require viral suppression within the past 6 months

Some may have viremia and resistance to 3TC and/or TDF at the time of switch
What can we learn from DAWNING?

- Participants failing NNRTI-based first-line
- 2 out of 314 subjects developed resistance to DTG

All subjects were required to have at least one active NRTI

Is DTG effective with no active NRTIs?

- DTG monotherapy clinical trials
  - DOMONO
  - DOLAM
  - MONCAY

7 out of 204 participants demonstrated treatment emergent DTG resistance

Is DTG effective with no active NRTIs?

- DTG monotherapy clinical trials
  - DOMONO
  - DOLAM
  - MONCAY

7 out of 204 participants demonstrated treatment emergent DTG resistance

Functional monotherapy could compromise the effectiveness of TLD

Outline

• A new era for global ART
• Introduction to integrase inhibitors
• Is dolutegravir (DTG) resistance-proof?
• **Potential barriers to adherence to DTG**
• Key questions for the research community
Potential Adherence Challenges

• Patient-level
• System-level
Neuropsychiatric Effects

Neuropsychiatric Effects

• Possible learning and memory deficits associated with integrase inhibitors

DTG and Neural Tube Defects

Messaging regarding birth defects

- How does the messaging influence adherence?
- If the update shows no increased risk, will there still be hesitancy from patients and providers?
Potential Adherence Challenges

- Patient-level
- System-level
Stock Concerns for DTG

• Pace of roll-out

• Twice daily DTG needed for those on concurrent TB treatment
  – Requires DTG single tablets
  – Higher risk of stock-outs for non-fixed dose combination tablets
Outline

• A new era for global ART
• Introduction to integrase inhibitors
• Is dolutegravir (DTG) resistance-proof?
• Potential barriers to adherence
• Key questions for the research community
How forgiving is DTG?
Optimal adherence threshold

• Often discussed 95% adherence threshold was for un-boosted protease inhibitors

• Is there a more forgiving threshold for DTG-based regimens?

What should our messaging be about DTG, adherence, and resistance?
Should adherence measures be included in monitoring effectiveness of TLD?
How should we monitor?

Current WHO Algorithm

- VL >1000
  - Intensified counseling
  - Repeat VL
    - Repeat VL <1000
      - Continue 1st line
    - Repeat VL >1000
      - Change to 2nd line

This algorithm was designed for NNRTI-based regimens

How should we monitor?

Should an adherence test be included?

- **VL >1000**
  - Intensified counseling
  - Repeat VL
    - Repeat VL <1000
      - Continue 1st line
    - Repeat VL >1000
      - Change to 2nd line

Data to watch for:

• ADVANCE
• Update on neural tube defects and DTG
• Updates from national programs
• TLD implementation studies
DISCO: A TLD Implementation Study

- Prospective observational cohort study
- Began enrollment in May 2019
- Rural sites in Uganda and South Africa
- Overarching aim:
  - Evaluate the effects of pre-existing resistance and adherence on TLD effectiveness
Acknowledgements

• Jessica Haberer, MD MS
• Mark Siedner, MD MPH
• Mwebesa Bwana, MBChB
• Winnie Muyindike, MBChB

• NIAID
  – K23 AI143470
  – R21 AI145537
• Harvard University CFAR
  – P30 AI060354
• MGH ECOR Fund for Medical Discovery
  – Clinical Research Fellowship
• Gilead Sciences
  – Research Scholars Program in HIV
• ViiV Healthcare
  – Investigator sponsored research