Roche

It takes more than just a single target

As the challenges you face evolve...

HIV mutates

"No HIV-1 mutation can be considered to be neutral"[1]

- Growing evidence indicates all HIV subtypes may be prone to errors; posing enormous challenges to viral load monitoring.[2]
- HIV-1 diversity is increasing and recombinants of greater complexity are being created.[1,3]
  - Produces 10^{10} virions / day.[4]
  - Creates a polymorphism every 2,000–5,000 nucleotides.[4]
- Drug pressure and polymorphisms can lead to RT-PCR inefficiency.[2,3,5–7]
- Mismatches and mutations unseen by single target assays can lead to underquantification.[3,6]

Underquantification can have major clinical repercussions; delaying the detection of drug resistance[2,3]

Treatments evolve

Newer classes of medications change treatment regimens

- European, US and International guidelines recommend integrase inhibitors for 1st line therapy.[8,9, 25]
- In 2012, the use of raltegravir increased 25%.[10]
- The integrase gene is an attractive target for drug development.[11]
  - Raltegravir is approved for global use.
  - Elvitegravir is approved for use in the US and is under review in Europe.
  - Dolutegravir under regulatory review in the US, Europe, and Japan.
  - Additional compounds are in development.

Drug resistance remains a central problem

- Associated with all antiretrovirals, including integrase inhibitors.[12–15]
- Over 42 mutations are associated with resistance to raltegravir.[16,17]

Selective pressure on a drug target has the potential to compromise treatment efficacy.[11]

So does Roche and the support we provide.

Two targets

"Represents an important step forward" [5]

- Targeting two regions improves genotype inclusivity, detects HIV-1 variants and potentially avoids underquantific tion.[5,6,18]
  - 30 samples not quantifie by the single target assay were quantifie by the Roche dual target HIV-1 assay.[5]
  - The single target comparator assay quantifie 19% of samples significantl lower than the Roche dual target HIV-1 assay.[3]
- Amplific tion of a less ideal target region might explain discrepancies already observed in the literature.[3,5,6,18]

Accurately quantifying HIV-1 RNA with a dual target assay contributes to optimal treatment decisions for patient management [2,5,18,19]

Superior sensitivity

"Evolution of viral resistance can occur in the setting of low-level viremia" [8,11]

- Two clinical trials and a cohort analysis detected new resistance mutations in 37% and 65% respectively of patients who had developed persistent low-level viremia.[8,20,21]
- Viremia between 20–49 RNA copies/mL have been associated with higher baseline viral load and less time on ART.[22,23]
- Quantifying HIV-1 viremia between 20–49 copies/mL may have value.[19,22]

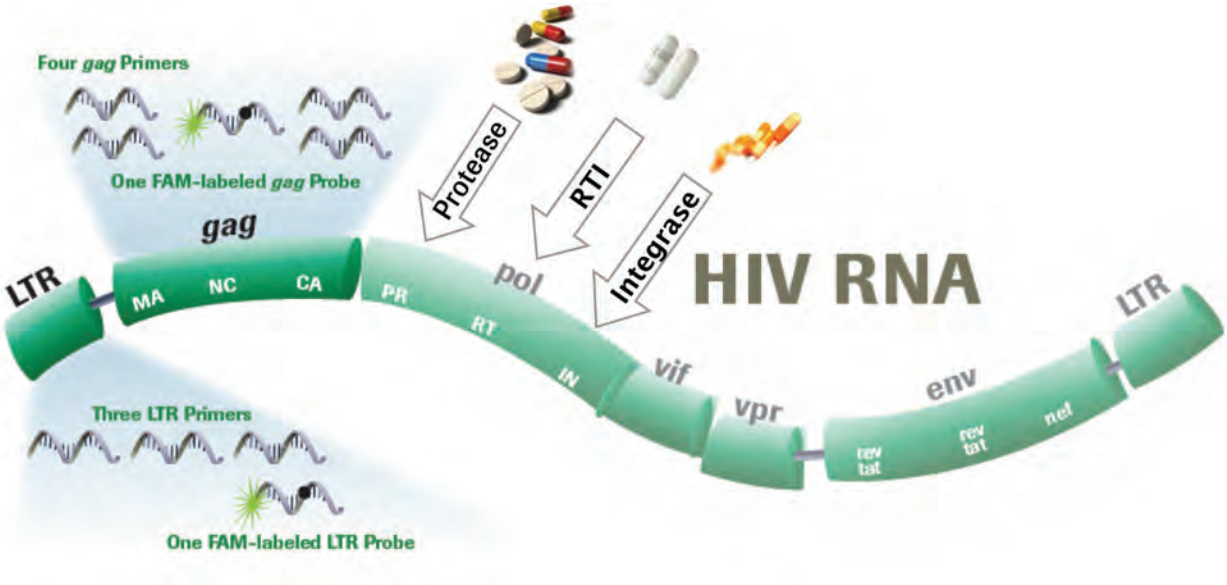
Sensitive assays provide insight into disease awareness, assist in research eradication efforts, and may lead to improvements in disease management for patients living with the HIV-1 virus[3,18]

Stay one step ahead

*With the COBAS® AmpliPrep/COBAS TaqMan® HIV-1 Test v2.0 and the COBAS TaqMan® HIV-1 Test, v2.0 for use with the High Pure System**

Performance for today; prepared for tomorrow

It takes more than just a single target to stay ahead of HIV-1. A diversifi d approach includes multiple safeguards, such as a dual target and increased sensitivity, providing confi ence in test results for patients living with the HIV-1 virus[2,5,22–24]



*This test is intended for use in conjunction with clinical presentation and other laboratory markers of disease progress for the clinical management of HIV-1 infected patients. The test can be used to assess patient prognosis by measuring the baseline HIV-1 RNA level or to monitor the effects of antiretroviral therapy by measuring changes in EDTA plasma HIV-1 RNA levels during the course of antiretroviral treatment.

References:

1. Mansky LM. Retrovirus mutation rates and their role in genetic variation. J Gen Virol. 1998; 79: 1337–1345.
2. Pyne MT ***et al***. Large-scale comparison of Roche Cobas AmpliPrep/Cobas TaqMan and Abbott RealTime HIV assays. J of Vir Methods. 2012; 184: 106-108.
3. Sire JM ***et al***. Comparative RNA quantification of HIV-1 Group M and non-M with the Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 v2.0 and Abbott Real-Time HIV-1 PCR assays. J Acquir Immune Defic Syndr. 2001; 56: 239-243.
4. Loeb LA ***et al***. Lethal mutagenesis of HIV with mutagenic nucleoside analogs. Proc Natl Acad Sci U S A. 1999; 96: 1492–1497.
5. Paba P et al. Performance evaluation of the COBAS/TaqMan HIV-1 v2.0 in HIV-1 positive patients with low viral load: A comparative study. J Virol Methods. 2011; 173: 399-402.
6. Damond F ***et al***. Evaluation of an upgraded version of the HIV-1 test for HIV-1 load quantification. J Clin Microbiol. 2010; 48: 1413-1416.
7. Church D ***et al***. Comparison of the RealTime HIV-1, COBAS TaqMan 48 v1.0, Easy Q v1.2, and Versant v3.0 assays for determination of HIV-1 viral loads in a cohort of Canadian patients with diverse diverse HIV subtype infections. J Clin Microbol. 2011; 49: 118-124.
8. Thompson MA ***et al***. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA. 2012; 308: 387-402.
9. HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf, accessed December 21 2012.
10. Annual Report, Merck & CO., INC. Franchise / Key Product Sales, September Year-To-Date 2012, Table 3b.
11. Goethals O ***et al***. Resistance to raltegravir highlights integrase mutations at codon 148 in conferring cross-resistance to a second-generation HIV-1 integrase inhibitor. Antiviral Res. 2011; 91: 167-176.
12. Wainberg MA ***et al***. The development of novel HIV integrase inhibitors and the problem of drug resistance. Curr Opin Virol. 2012; 2: 656-662.
13. Underwood MR ***et al***. The activity of the integrase inhibitor dolutegravir against HIV-1 variants isolated from raltegravir-treated adults. J Acquir Immune Defic Syndr. 2012; 61: 297-301.
14. Gottuzzo E ***et al***. Sustained efficacy and safety of raltegravir after 5 years of combination antiretroviral therapy as initial treatment of HIV-1 infection: final results of a randomized, controlled, phase II study (Protocol 004). J Acquir Immune Defic Syndr. 2012; 61: 73-77.
15. Malet I ***et al***. Mutations associated with failure of raltegravir treatment affect integrase sensitivity to the inhibitor in vitro. Antimicrob Agents Chemother. 2008; 52: 1351-1358.
16. Ceccherini-Silberstein F ***et al***. Characterization and structural analysis of HIV-1 integrase conservation. AIDS Rev. 2009 Jan-Mar; 11: 17-29.
17. Latallaide M ***et al***. Natural polymorphism of the HIV-1 integrase gene and mutations associated with integrase inhibitor resistance. Antivir Ther. 2007; 12: 563-570.
18. Wojewoda CM ***et al***. Comparison of Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 test version 2.0 (CAP/CTM v2.0) with other real-time PCR assays in HIV-1 monitoring and follow-up of low-level viral loads. J Virol Methods. 2013; 187: 1-5.
19. Pas S ***et al***. Performance evaluation of the new Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 test version 2.0 for quantification of human immunodeficiency virus type 1 RNA. J Clin Microbol. 2010; 48: 1195–1200.
20. von Wyl V ***et al***. Swiss HIV Cohort Study. Incidence of HIV-1 drug resistance among antiretroviral treatment-naive individuals starting modern therapy combinations. Clin Infect Dis. 2012; 54: 131-140.
21. Taiwo B ***et al***. Antiretroviral drug resistance in HIV-1-infected patients experiencing persistent low-level viremia during first-line therapy. J Infect Dis. 2011; 204: 515-520.
22. Pascual-Pareja JF ***et al***. Detection of HIV-1 at between 20 and 49 copies per milliliter by the Cobas TaqMan HIV-1 v2.0 assay is associated with higher pretherapy viral load and less time on antiretroviral therapy. J Clin Microbiol. 2010; 48: 1911-1912.
23. Maggiolo F ***et al***. Ultrasensitive assessment of residual low-level HIV viremia in HAART treated patients and risk of virological failure. J Acquir Immune Defic Syndr. 2012; 60: 473-482.
24. Doyle T ***et al***. Plasma HIV-1RNA detection below 50 copies/ml and risk of virologic rebound in patients receiving highly active antiretroviral therapy. Clin Infect Dis. 2012; 54: 724-732.
25. EACS Guidelines v6.1, edition 2, November 2012, page 12

Roche Diagnostics
Scandinavia AB Box 1228
171 23 Solna
PM2019-00513

07020864001 ① 0313 - 2. WW