Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix. Recommendations Development Process

I. Brief Summary

The recommendations for antiretroviral therapy in adults with HIV infection recommendations were developed by an international panel of experts in HIV research and patient care. The Panel was established initially in 1995 by the International Antiviral Society–USA (IAS–USA)\(^1\); members are selected by the IAS–USA Board of Directors and vetted by the organization for suitability for the panel. Panel members serve in a volunteer (uncompensated) capacity and do not participate in industry promotional activities such as speakers’ bureaus, lectures, or other marketing activities during their tenure on the panel. Members of the current panel convened in person and by conference calls from 2015 to mid-2016. The chair (Huldrych F. Günthard, MD) oversees the discussions of the process and evidence review and manuscript development, and guides the group to consensus. Section leaders (eBox 3) and teams were appointed to evaluate evidence and summarize panel discussions for each section. Prior to selection of the section teams and leaders, panel members declared their financial relationships with commercial concerns, discussed potential conflicts of interest (COIs), and recused themselves from serving as section leaders or team members as necessary.

Evidence considered for updating the recommendations was limited to data published in the scientific literature, presented at major peer-reviewed scientific conferences, or released as safety reports by regulatory agencies or data safety and monitoring boards, since the last update in 2014 through June 2016.\(^2\) Literature searches were conducted by a systematic review methodologist at the University of California San Francisco. The publication list was reviewed by a panel member (Paul A. Volberding, MD) for relevance. Approximately 320 citations were ultimately identified from an initial list of more than 3200 in the initial search strategy. Relevant abstracts publically presented at recent scientific conferences were identified by panel members. Manufacturers of antiretroviral drugs were asked to submit lists of relevant publications or abstracts meeting the established criteria. All reference lists, published papers, abstracts, and other relevant reports were organized and stored on a web-based, shared, electronic drive to which all panel members have ongoing access.

These recommendations focus on HIV-1–infected adults in international, developed-world settings where antiretroviral drugs are generally available (approved by regulatory bodies or in expanded access) or in late-stage development (new drug application filed). Recommendations were made by full-panel consensus and rated according to the strength of the recommendation and the quality of the supporting evidence (Manuscript Table 1). For areas in which recommendations have not changed substantially or no or few new data are available, the reader is referred to the previous report.\(^3\)

II. Detailed Summary

a. Background

The medical management of HIV changes rapidly, owing to the continued rapid advances in pathogenic and clinical knowledge leading to necessary changes in patient care, as well as ongoing availability of new drugs, formulations, and laboratory testing to optimally manage HIV infection. In 1995, on recognizing the rapidly changing knowledge base, the complexity of HIV management and expertise needed to provide quality care, and the lack of current plans to update any existing HIV guidelines, the need to disseminate reliable evidence-based guidance for clinicians involved in HIV management was clear. The IAS–USA Antiretroviral Recommendations Panel was established in 1995 by the IAS–USA to develop this needed guidance for physicians and other clinicians actively involved in HIV care.
b. The IAS–USA and Its Role in the Recommendations

The IAS–USA is a 501(c)(3) not-for-profit, mission-based, nonmembership, educational organization that was established in 1992. The mission of the IAS–USA is to improve the treatment, care, and quality of life for people with HIV, hepatitis C virus (HCV), or other viral infections through high-quality, relevant, balanced, and needs-oriented education and information for practitioners who are actively involved in medical care. The IAS–USA delivers annual continuing medical education (CME) programs on HIV and HCV that include live courses; live intensive, interactive workshops; live webinars; online interactive activities in the series Cases on the Web (COW); and the peer-reviewed, indexed journal Topics in Antiviral Medicine. In addition, IAS–USA manages and serves as the CME sponsor for the annual Conference on Retroviruses and Opportunistic Infections (CROI), a research conference. The IAS–USA is accredited with commendation by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

IAS–USA has sponsored the development of evidence-based recommendations for viral load monitoring, antiretroviral therapy, HIV drug resistance testing, cytomegalovirus (CMV) infection, and the metabolic complications of antiretroviral therapy, all of which are published in the medical literature. In addition to the published recommendations, the IAS–USA served as the collaborating partner for the American Association for the Study of Liver Diseases (AASLD)/Infection Diseases Society of America (IDSA)/IAS–USA HCV Guidance (www.HCVguidelines.org) from its inception until January 2016.

The volunteer members of the IAS–USA Board of Directors (eBox 1) oversee the development of the information and educational programs and are not compensated for their roles in oversight and governance of the organization.

IAS–USA funding comes from a variety of sources. Largest single source of revenue is conference and CME participant registration fees. Other funding sources include grants from the pharmaceutical/diagnostics (commercial) industries, grants and subcontracts from government agencies, private donations, and gifts-in-kind from local community businesses and individuals. The commercial support that IAS–USA accepts is only for selected activities. Two large national CME efforts (one on HIV and another on HCV) invite funding in the form of educational grants from industry. Per IAS–USA policy, any effort that uses commercial grants must receive grants from several companies with competing products. Funds are pooled and distributed to activities within the effort at the sole discretion of the IAS–USA. Funders have no input into any activity, including its content, development, or selection of topics or speaker(s). Funders are listed in each activity as applicable.

The development of the Antiretroviral Therapy Recommendations is supported and funded by the IAS–USA. The IAS–USA determined the need for updated recommendations; selected panel members based on expertise in research and care to represent developed-world settings affected by HIV disease; determined the most appropriate way in which to disseminate the information (eg, publication in a medical journal rather than publication in the IAS–USA journal, web publication, etc); and provided administrative oversight and financial support.

The Panel itself is responsible for proposing the design and conduct of the work; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript. IAS–USA provided staff support for administrative management, oversight of literature searches and editorial and production assistance. At least one member of the Board serves in each panel to ensure continuing with the IAS–USA mission.

c. Identifying and Screening Panel Members

The panel was initially appointed in 1995, and members have rotated periodically since then. In evaluating potential participants for the Panel, the IAS–USA Board considered individuals who 1) are recognized as authorities in HIV treatment research and clinical care, 2) have appointments in major medical teaching or research institutions, 3) have a demonstrated ability to review and evaluate evidence in an effort to provide useful recommendations in the field, 4) meet the IAS–USA COI and financial relationship criteria for participation (see below and...
Like the IAS–USA Board of Directors, participants in IAS–USA panels are volunteers and receive no financial compensation for their panel participation. In joining the Panel, members agree to commit substantial time to the effort necessary for evidence review and for participation in the consensus process.

d. COI Management

It is the policy of IAS–USA to ensure balance, independence, objectivity, and scientific rigor in all its activities. All parties with control over the content of IAS–USA activities are required to disclose to the organization and activity audience any financial interest or other relationship with the manufacturer(s) of any commercial product(s) or provider(s) of commercial services with interests discussed in the activity (e.g., presentation, article, etc) within at least the past 12 months. Financial interests or other relationships can include receipt of grants or research support, status as employee or consultant, stock or options holder, paid lecturer, paid lecturer, writer, or author, or member of speakers bureau, of the party or of his or her spouse or partner. The ACCME defines a financial interest as an interest of any dollar amount. Part of the IAS–USA policies to ensure the integrity of its activities is the policy to separate commercial promotion from core IAS–USA educational and informational activities. Individuals who conduct marketing or promotional activities for commercial firms may not contribute to core IAS–USA programs. A marketing or promotional activity includes any activity in which the commercial entity controls key elements, such as speaker or topic selection, that could be used to serve the entity’s commercial interests (e.g., speakers bureaus, advertorials, etc). Individuals may not participate in most IAS–USA programs for 12 months after functioning in a promotional or marketing effort for a commercial firm. A notable exception to the separation policy is the annual Conference on Retroviruses and Opportunistic Infections (CROI) which allows research and symposia presentations by individuals with some of such relationships (including employment) because of its large focus on the presentations on original research, if their research or work passes rigorous peer review). Panel members who meet general criteria and are appointed, agree not to participate in any promotional activity on behalf of a pharmaceutical or medical device company (e.g., serve on a speaker bureau, as a paid lecturer, or a similar contribution) while a member of the panel. Any conforming financial relationships with commercial entities that still may represent a real or potential COIs, will be resolved so that they do not influence the content of the recommendations. Prior to selection of the section teams and leaders, panel members declared their financial relationships with commercial concerns, discussed potential COIs, and recused themselves from serving as section leaders or team members accordingly.

III. The IAS–USA Antiretroviral Recommendations Panel

The members of the IAS–USA Antiretroviral Recommendations Panel are listed in eBox 2. The Panel convened in person in 2015 to mid-2016, and regularly by conference call. The chair oversees the discussions of the process and evidence review and manuscript development, and guides the group to consensus. Section leaders and teams were appointed to evaluate evidence and summarize panel discussions for each section.

IV. Rating the Recommendations

The Panel is divided by topic into working sections, each with a section leader. These sections are responsible for reviewing and screening evidence, developing preliminary recommendations, and presenting these to the full Panel for discussion, identification of further evidence, and consensus.
The selected rating system (Manuscript eTable 1) combines 2 ratings for each recommendation. One rates the strength of the recommendation (strong, moderate, or limited support) and the other rates the quality of the evidence (ranging from Ia, based on evidence from 1 or more randomized controlled clinical trial[s] published in the peer-reviewed literature, to III, based on the Panel’s analysis of the accumulated available evidence).

V. Content of the Recommendations

The Panel agreed on the purpose, audience, and scope of these recommendations and on 8 main content sections (and subsections).

Content Sections:

1. When to Start
2. Recommended Initial Regimens
3. The Interface of Antiretroviral Therapy and Opportunistic Infections
4. When and What to Switch
5. Laboratory Monitoring
6. Engagement in Care and ART Adherence
7. Prevention
8. Future Directions

Panel members were assigned to content sections based on their expertise and section leaders were appointed (eBox 3). The Panel Chair participates in all sections and reviews the entire manuscript, and Paul A. Volberding, MD, reviewed literature search results and identified relevant publications, and also reviewed the entire manuscript.

From 2015 to mid-2016, sections met in person and by conference call and e-mail exchange. Initial discussions were used to develop detailed Section outlines, and assign participants to draft subsections. The full Panel reviewed sections and the final manuscript.

VI. Evidence Collection and Literature Searches

Panel members were selected based on their active work in the field of HIV research and care, and detailed knowledge of available evidence (published and presented at major scientific conferences).

Literature searches in PubMed and Embase were conducted and designed by an expert in systematic reviews, Hacsi Horvath and one of the panel members, Paul Volberding (eTable 1). The initial literature search provided data available since the 2014 publication of the recommendations through April 2016; approximately 320 references were ultimately identified. Relevant abstracts publically presented at recent scientific conferences were identified by panel members. All manufacturers of FDA-approved antiretroviral drugs were asked to submit lists of publications or abstracts meeting the established criteria (eTable 2). Drug manufacturers were instructed to provide references and electronic copies of the published or presented papers or abstracts only and not to comment on the design, methods, results or implications of any of the work. All reference lists, published papers, abstracts, and other relevant reports were organized and stored on a web-based, shared, electronic drive to which all panel members have ongoing access.
References

Ref ID: 795

Ref ID: 13436

Ref ID: 11418

Ref ID: 989

Ref ID: 1382

Ref ID: 1978

Ref ID: 7755

Ref ID: 6062

Ref ID: 9521

Ref ID: 4066

Ref ID: 5128

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Ref ID: 1304

Ref ID: 2244

Ref ID: 4617

Ref ID: 7276

Ref ID: 3494

Ref ID: 1393

Ref ID: 836

Ref ID: 2330

Ref ID: 11289
eBox 1. Volunteer IAS–USA Board of Directors, June 2016

Paul A. Volberding, MD  
Professor of Medicine  
Co-Director, Center for AIDS Research  
Director, AIDS Research Institute  
Director of Research, Global Health Sciences  
University of California San Francisco  
San Francisco, California

Constance A. Benson, MD  
Professor of Medicine  
Divisions of Infectious Diseases and Global Public Health  
Infectious Diseases Training Program Director  
Director, Antiviral Research Center  
PI/Director, HIV/AIDS Clinical Trials Unit  
University of California San Diego  
School of Medicine  
San Diego, California

Peter C. Cassat, JD  
Vice President and General Counsel  
AutoTrader.com  
Atlanta, Georgia

Judith S. Currier, MD  
Professor of Medicine  
Chief, Division of Infectious Diseases  
Associate Director, Clinical AIDS Research and Education (CARE) Center  
David Geffen School of Medicine  
University of California Los Angeles  
Los Angeles, California

Carlos del Rio, MD  
Professor of Global Health  
Rollins School of Public Health  
Professor of Medicine  
Emory University School of Medicine  
Atlanta, Georgia

Joel E. Gallant, MD, MPH  
Medical Director of Specialty Services  
Southwest CARE Center  
Santa Fe, New Mexico  
Clinical Professor of Medicine  
Division of Infectious Diseases  
University of New Mexico School of Medicine  
Albuquerque, New Mexico

Roy M. Gulick, MD, MPH  
Rochelle Belfer Professor of Medicine  
Chief, Division of Infectious Diseases  
Weill Medical College of Cornell University  
New York, New York

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IAS–USA
Executive Manager
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Birmingham, Alabama

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Professor of Pathology and Medicine
University of California San Diego and
Veterans Affairs San Diego Healthcare System
San Diego, California

Michael S. Saag, MD
Professor of Medicine
Jim Straley Chair in AIDS Research
Director, Center for AIDS Research
Associate Dean for Global Health, School of Medicine
University of Alabama at Birmingham
Birmingham, Alabama

Robert T. Schooley, MD
Professor and Vice Chair of Medicine
Head, Division of Infectious Diseases
University of California San Diego
La Jolla, California
eBox 2. IAS–USA Antiretroviral Therapy Recommendations Panel

Huldrych F. Günthard, MD (Panel Chair)
Professor of Infectious Diseases
President of the Swiss HIV Cohort Study
Deputy Chief, Division of Infectious Diseases and Hospital Epidemiology
University Hospital Zurich
Zurich, Switzerland

Constance A. Benson, MD*
Professor of Medicine
Director, Infectious Disease Training Program
Director, Antiviral Research Center
Principal Investigator/Director, HIV/AIDS Clinical Trials Unit
University of California San Diego
San Diego, California

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Professor of Global Health
Rollins School of Public Health
Professor of Medicine
Emory University School of Medicine
Atlanta, Georgia

Joel E. Gallant, MD, MPH*
Medical Director of Specialty Services
Southwest CARE Center
Santa Fe, New Mexico
Clinical Professor of Medicine
Division of Infectious Diseases
University of New Mexico School of Medicine
Albuquerque, New Mexico

Rajesh T. Gandhi, MD
Associate Professor of Medicine Harvard Medical School
Boston, Massachusetts

Joseph J. Eron, MD
Professor of Medicine and Epidemiology
Principal Investigator, AIDS Clinical Research Group
The University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Jennifer F. Hoy, MBBS
Professor of Medicine
The Alfred Hospital
Monash University
Melbourne, Australia

Raphael J. Landovitz, MD
Associate Professor of Medicine
David Geffen School of Medicine
University of California Los Angeles Center for Clinical AIDS Research and Education
Los Angeles, California
eBox 3. Working Sections of the IAS–USA Antiretroviral Therapy Recommendations Panel

When to Start
   Section Team: Jennifer F. Hoy, MBBS (Leader); Constance A. Benson

Interface Between Antiretroviral Therapy and Opportunistic Infections
   Section Team: Constance A. Benson, MD (Leader); Jennifer F. Hoy, MBBS; Melanie A. Thompson, MD

Recommended Initial Regimens
   Section Team: Paul E. Sax, MD (Leader); Rajesh T. Gandhi, MD; Michael S. Saag, MD

When and How to Switch
   Section Team: Joel E. Gallant, MD, MPH (Leader); Michael S. Saag, MD

Laboratory Monitoring
   Section Team: Melanie A. Thompson, MD (Leader); Jennifer F. Hoy, MBBS; Constance A. Benson, MD

Engagement in Care and ART Adherence
   Section Team: Michael J. Mugavero, MD, MHSc (Leader); Carlos del Río, MD; Melanie A. Thompson, MD

Prevention
   Section Team: Carlos del Río, MD (Leader); Raphael J. Landovitz, MD

Future Directions
   Section Team: Joseph J. Eron, MD (Leader); Davey M. Smith, MD
## eTable 1. Summary of Evidence Collection

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<td>• Panel members’ identification*</td>
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<td>Number of relevant references reported in manuscript (submitted June 10, 2016)</td>
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*Of note, individual panel members collected relevant evidence throughout the process and reviewed materials submitted by manufacturers (particularly for safety issues) and this process cannot be quantified.
**Table 2. Search Terms Used and Results of Embase and PubMed Literature Searches**

**INITIAL SEARCH STRATEGY**

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- Pooling Embase and PubMed results for 6/24/14 through 2016 (including “ahead of print” records): 4223 records
  - Removed 905 duplicates: There are 3318 unique records for that period
- Pooling search results for 2/1/16 through 3/1/16: 207 records
  - Remove 24 duplicates: There are 183 unique records for that period

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# Search | Embase Query | Results |
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| #2 | 'patient'/exp OR 'patient' OR 'patient'/de OR OR patient OR 'patients'/exp OR 'patients' OR 'patients'/de OR patients OR participant OR participants OR 'adult'/exp OR 'adult' OR 'adult'/de OR adult OR adults OR 'pregnant women'/exp OR 'pregnant women'/de OR 'pregnant women' OR 'research subjects'/exp OR 'research subjects'/de OR 'research subjects' OR 'art-naive' OR 'art-experienced' |
| #3 | 'clinical trial'/exp OR 'cohort analysis'/exp OR 'comparative study'/exp OR 'controlled clinical trial'/exp OR 'controlled study'/exp OR 'double blind procedure'/exp OR 'major clinical study'/exp OR 'multicenter study'/exp OR 'prospective study'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'randomized':ab,ti OR 'randomised':ab,ti OR 'randomly':ab,ti OR 'cohort':ab,ti OR 'trial':ab,ti OR 'groups':ab,ti OR 'compared':ab,ti OR 'versus':ab,ti OR 'vs':ab,ti OR 'noninferiority' OR 'non-inferiority' OR 'blind' OR 'open label' |

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<th>PubMed Query</th>
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<td>#7</td>
<td>Search #6 AND Publication date from 2014/06/24 to 2016/12/31</td>
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<td>#6</td>
<td>Search #1 AND #2 AND #3 AND #4 AND #5</td>
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<td>Search human immunodeficiency virus OR human immune deficiency virus OR acquired immunodeficiency syndrome OR acquired immune deficiency syndrome OR hiv* OR HIV/AIDS OR HIV-1</td>
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<td>Search &quot;Dideoxynucleosides&quot;[nm] OR nucleoside reverse transcriptase inhibitor[mh] OR nucleoside reverse transcriptase inhibitor OR non-nucleoside reverse transcriptase inhibitor[mh] OR non-nucleoside reverse transcriptase inhibitor OR NRTI OR NNRTI OR protease inhibitor[mh] OR protease inhibitor OR integrase inhibitor[mh] OR INSTI OR integrase inhibitor OR chemokine receptor antagonist[mh] OR “chemokine receptor antagonist” OR crf5 OR fusion inhibitor OR abacavir OR amprenavir OR atazanavir OR cobicistat OR darunavir OR delavirdine OR didanosine OR dolutegravir OR efavirenz OR elvitegravir OR emtricitabine OR etravirine OR fosamprenavir OR indinavir OR lamivudine OR lopinavir OR nelfinavir OR nevirapine OR raltegravir OR ripivirine OR rilronavir OR saquinavir OR stavudine OR tenofovir OR tipranavir OR zidovudine OR 3tc OR abc OR apv OR atv OR atv/c OR atv/r OR cobi OR d4t OR ddc OR ddi OR dlv OR drv OR drv/c OR dv/r OR dtg OR efv OR efv/c/tdf/ftc OR etr OR evg OR evg/c OR evg/c/tdf/ftc OR evg/r OR fpv OR fpv/r OR ftc OR idv OR lpv OR lvp/r OR mvc OR nfv OR nvp OR pi/c OR pi/r OR ral OR rpv OR rtv OR sqv OR sqv/r OR tdf OR tpv OR tpv/r OR zdv OR zdv OR zid OR aptivus OR aptivus OR crixivan OR crixivan OR descovy OR edurant OR edurant OR emtriva OR emtriva OR epivir OR epivir OR fuzon OR fuzon OR inteline OR inteline OR invirase OR invirase</td>
<td>330674</td>
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†1910 total results (n=1701 results after removing 209 duplicates).

‡Merged with results from April 5, 2016, and removed 282 already-seen records: 1419 remain; from these removed 141 studies from low- and middle-income countries and 60 studies of pediatric patient populations (n=1218 to screen).
<table>
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<th>Manufacturer</th>
<th>Information Requested</th>
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<th>Date Received</th>
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| AbbVie                | • Presented at national or international conferences or has been published in the peer-reviewed literature  
• Data should be from prospective clinical trials (ie, properly randomized controlled trials), cohort studies, and ancillary trials (pharmacologic and drug interaction studies)  
• Any information about newly recognized toxicities and complications associated with your product(s) would be helpful.                                                                                           | 03/14/2016     | 03/28/2016     |
| Bristol-Myers Squibb  | • Presented at national or international conferences or has been published in the peer-reviewed literature  
• Data should be from prospective clinical trials (ie, properly randomized controlled trials), cohort studies, and ancillary trials (pharmacologic and drug interaction studies)  
• Any information about newly recognized toxicities and complications associated with your product(s) would be helpful.                                                                                           | 03/14/2016     | 03/31/2016     |
| Gilead Sciences, Inc  | • Presented at national or international conferences or has been published in the peer-reviewed literature  
• Data should be from prospective clinical trials (ie, properly randomized controlled trials), cohort studies, and ancillary trials (pharmacologic and drug interaction studies)  
• Any information about newly recognized toxicities and complications associated with your product(s) would be helpful.                                                                                           | 03/14/2016     | 04/01/2016  
|                       |                                                                                      |                | 05/04/2016     |
| Janssen Therapeutics  | • Presented at national or international conferences or has been published in the peer-reviewed literature  
• Data should be from prospective clinical trials (ie, properly randomized controlled trials), cohort studies, and ancillary trials (pharmacologic and drug interaction studies)  
• Any information about newly recognized toxicities and complications associated with your product(s) would be helpful.                                                                                           | 03/14/2016     | 04/01/2016     |
| Merck & Co, Inc       | • Presented at national or international conferences or has been published in the peer-reviewed literature  
• Data should be from prospective clinical trials (ie, properly randomized controlled trials), cohort studies, and ancillary trials (pharmacologic and drug interaction studies)  
• Any information about newly recognized toxicities and complications associated with your product(s) would be helpful.                                                                                           | 03/14/2016     | 04/01/2016     |
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| Genentech        | • Presented at national or international conferences or has been published in the peer-reviewed literature  
                  • Data should be from prospective clinical trials (ie, properly randomized controlled trials), cohort studies, and ancillary trials (pharmacologic and drug interaction studies)  
                  • Any information about newly recognized toxicities and complications associated with your product(s) would be helpful. | 03/14/2016 03/18/2016 |
| ViiV Healthcare  | • Presented at national or international conferences or has been published in the peer-reviewed literature  
                  • Data should be from prospective clinical trials (ie, properly randomized controlled trials), cohort studies, and ancillary trials (pharmacologic and drug interaction studies)  
                  • Any information about newly recognized toxicities and complications associated with your product(s) would be helpful. | 03/14/2016 03/31/2016 |