SUPLEMENTO ESPECIAL
HIV TREATERS MEDICAL ASSOCIATION OF PUERTO RICO

Mensaje de la Presidenta

Estimados colegas

El temas del VIH es un asunto que aún no se ha solucionado. Sigue siendo un problema de salud pública en Puerto Rico así como en muchos lugares del planeta. Por tal razón, ofrecemos algunos temas de interés para ustedes y de ayuda en su práctica. Todos deseamos ser parte de la solución y conocer más sobre esto, por lo que los invitamos a nuestra 14ª Convención, donde estaremos discutiendo temas de relevancia tanto para el tratamiento del VIH como para otras condiciones.

Por un Puerto Rico con cero contagios, date la oportunidad de conocer más sobre el VIH y sus otras caras. Recuerda que el conocimiento es poder, y que el poder nos da control para poder ayudar a nuestros pacientes que ya viven con VIH, así como para orientar y prevenir a aquellos que no lo tienen.
Te esperamos.

Vilmary Sierra-Rosa, MD, AAHIVS
Presidenta de la Asociación de Médicos Tratantes de VIH en Puerto Rico

14th Annual Puerto Rico HIV Treaters Medical Association Convention
HATS - "Holistic Approach for Treatment Success"
November 5 - 8, 2015
Dorado Embassy Suites, Dorado, PR

Thursday, Nov. 5	**Pre – Course:** Administration, Management and Control of Antibiotics (3 CME Credits) Bioethics and Professionalism (6 CME Credits)
7:00-8:00am	Registration
8:00-10:00am	**Administration and Management of Antibiotics** Carlos Guzman,MD
10:00-10:15pm	Break
10:15-11:15pm	**Control of Antibiotics** Carlos Guzman,MD
11:15-12:00pm	Registration & light lunch
12:00-4:00pm	**Bioethics Overview** Rafael Bready,MD
4:00-4:15pm	Break
4:15-6:15pm	**Professionalism Overview** Rafael Bready,MD
Friday, Nov. 6	**Pre – Course:** Autism (6 CME Credits)
7:00-8:30am	Registration
7:00-8:00am	**Neurologic introduction and evaluation** TBD
8:00-9:00am	**Development of the autistic child** TBD
9:00-9:15am	Break
9:15-10:15am	**Autism spectrum disorder evaluation** TBD
10:15-11:15am	**Alternative methods of intervention for autistic child** Giovanni Martínez, PhD
11:15-12:15md	**Autism: Issues and controversies of transition from adolescent to adult life** Giovanni Martínez, PhD
12:15-1:15pm	Lunch
1:15-2:15pm	**Autism: Issues and controversies of transition from adolescent to adult life** Giovanni Martínez, PhD
Friday, Nov. 6	**Scientific Program: Hats**
12:00-7:00pm	Registration
12:00-2:00pm	Lunch and Exhibits
2:00-2:15pm	Pre Test
2:15-3:00pm	**HIV Review: 30 years over the map** Iván Meléndez-Rivera, MD
3:00-3:45pm	**The weighty component of Drug Interactions Associated with HIV Medications on Clinical Care.** Kalumi Ayala, PharmD, AAHIVP
3:45-4:30pm	**"Getting to Zero" One Patient at a Time: HIV Prevention.** W. Jay Cuevas, MD
4:30-5:15pm	**HIV/AIDS: Therapy & Adherence** Ana M. Puga, MD
5:15-6:30pm	Break and Exhibits
6:30-7:00pm	**Opening Ceremony** Vilmary Sierra-Rosa, MD
7:00-8:00pm	**The Epidemiology of HIV and its Relevance to the Clinician** Iván Meléndez- Rivera, MD
8:00-8:15pm	Program Evaluation (Post Test)
8:15-10:00pm	Dinner
Saturday, Nov. 7	
7:00-12:00 MD	Registration
6:30-7:45am	Breakfast and Exhibits
7:45-8:00am	Pretest
8:00-9:00am	**Regimen Selection in HIV: Considering New Options to Optimize Outcomes** William Short, MD
9:00-10:00am	**The PI and Pharmacokinetic Enhancers in HIV Treatment: What You Need to Know** Sorana Segal-Maurer, MD
10:00-10:30am	Break & Exhibits
10:30-11:30am	**Decoding the Liver stage: Use and interpretation of serologic test and procedures for the liver.** Vilmary Sierra, MD
11:30-12:30md	**The New Shape on Hepatitis C treatment.** Henry González-Rivera, MD
12:30-1:30pm	Lunch & Exhibits
1:30-2:30pm	**Kidney Pathophysiology** Luis J. Quezada, MD
2:30-3:30pm	**Renal Aspects of the HIV Patient** Nelson Vallejo, MD
3:30-4:00pm	Break & Exhibits
4:00-5:00pm	**The 50 shades of gray on HIV** Claudia Martorell, MD
5:00-5:45pm	Program Evaluation
5:45-6:00pm	Closing at exhibit area
Sunday, Nov. 8	**Post – Course:** Administration Management and Control of Pain Management Drugs (3CME Credits)
7:00-9:00am	Breakfast & Registration
8:00-8:30am	Pre test
8:30-9:30am	**Patient with Special Needs** Muñeca Rivera, MD
9:30 – 10:30am	**The Epidemiology of pain I patients with HIV** Muñeca Rivera, MD
10:30-11:30am	**Update in acute pain management** Muñeca Rivera, MD
11:30-11:45am	Break
11:45-12:00md	Program evaluation and closing

Pre – Post Courses: 4 courses=18 credits. (Antibiotics = 3 credits; Bioethics = 6 credits; Autism = 6 credits; Pain Management = 3 credits).
Credit Designation: The Ponce School of Medicine submitted this live activity for a maximum of 11.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

For information & registration: Tel. (787) 646-0780

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Cuidado preconcepcional en mujeres con VIH:
Punto de partida para un embarazo exitoso

Vivian Tamayo-Agrait, MD, AAHIVMS, ABOG
Directora Médica PR-CoNCRA
Catedrática Auxiliar
Departamento de Obstetricia y Ginecología
Escuela de Medicina-UPR

Importancia de estrategias de prevención

La drástica disminución del riesgo de transmisión vertical del VIH ha sido uno de los avances más significativos en la historia de esta epidemia. Esto se debe a una serie de estrategias que, al utilizarse en conjunto, disminuyen el riesgo a menos del 1%. Sin estas intervenciones, la posibilidad de transmisión del virus de madre a hijo fluctúa entre un 30 y un 40%. El uso de terapia antirretroviral por la madre en el periodo anteparto y luego por el neonato como profilaxis postexposición disminuyen significativamente el riesgo de infección perinatal.

Las principales estrategias de prevención de transmisión vertical del VIH se pueden dividir en tres etapas: anteparto, intraparto y postparto. Aunque no se suele considerar parte del embarazo, el periodo preconcepcional es trascendental en el manejo de toda mujer en edad reproductiva, sobre todo en las que sufren de una condición crónica como el VIH.

Evaluación preconcepcional

La evaluación preconcepcional nos permite optimizar la salud de la mujer para que, de quedar embarazada, se disminuya lo más posible el riesgo de complicaciones durante el embarazo y para su infante. Es el momento de evaluar comorbilidades como hipertensión, diabetes, asma, hepatitis C, entre otras, y de manejarlas adecuadamente. Por ejemplo, la hepatitis C puede ser trasmitida perinatalmente y la coinfeccion con el VIH aumenta el riesgo de transmisión de ambas condiciones. Sin embargo, los fármacos recientemente aprobados para tratar la hepatitis C (que suelen tener una alta tasa de curación) no deben utilizarse durante el embarazo. Una mujer coinfectada con hepatitis C puede ser tratada para la misma y se retrasa un embarazo hasta que culmine ese tratamiento. Otras comorbilidades que pueden afectar adversamente un embarazo son la diabetes y la hipertensión. Lograr el control de estas antes de la gestación disminuye el riesgo de las complicaciones perinatales y obstétricas asociadas.

El periodo preconcepcional es también el momento indicado para evaluar los medicamentos utilizados por la mujer y sustituir los que tengan potencial teratogénico o sean contraindicados en un posible futuro embarazo. Ejemplos comunes de fármacos con potencial teratogénico son los inhibidores de la ECA (*ACE inhibitors*), algunos medicamentos contra la epilepsia y, en el caso del VIH, el fármaco efavirez. Además, es el momento para prescribir ácido fólico.

La evaluación preconcepcional nos permite también evaluar el perfil de vacunación de nuestra paciente y administrar las vacunas necesarias, algunas de las cuales, como la MMR y la vacuna de varicela, están contraindicadas durante el embarazo. Estas vacunas también poseen restricciones en su administración a pacientes inmusuprimidos. Ambas vacunas están con-

traindicadas en pacientes con CD4 menor de 200 y la de MMR está contraindicada si hay historial de alguna condición que defina el SIDA.

Por otro lado, por el riesgo de complicaciones fatales por infección con influenza durante el embarazo resulta importante que las mujeres en edades reproductivas y/o embarazadas reciban esta vacuna.

Durante el periodo preconcepcional, toda mujer debe ser evaluada y recibir educación y consejería sobre estilos de vida saludables. Por ejemplo, debe evaluarse el uso de sustancias nocivas como tabaco, alcohol y otras drogas tanto para mejorar su salud general como para evitar complicaciones asociadas al uso de las mismas durante el embarazo.

También se debe reforzar la importancia de mantener relaciones sexuales seguras para evitar la transmisión de otras enfermedades infecciosas, sobreinfección con el virus del VIH, y para proteger a su pareja sexual de la transmisión del mismo. Esta discusión debe incluir las alternativas reproductivas disponibles para las mujeres que viven con el VIH, que a su vez protegen a su pareja de la transmisión del virus. Algunas alternativas incluyen la autoinseminación, la inseminación artificial y el coito programado. Es importante tratar de incluir a la pareja de la paciente en dichas discusiones.

Evaluar terapia antirretroviral

En el caso particular del manejo del VIH, el periodo preconcepcional es el momento ideal para evaluar la terapia antirretroviral de la mujer en términos de su efectividad y seguridad durante un posible embarazo.

El valor de ofrecer medicamentos antirretrovirales en el periodo anteparto como estrategia de prevención de trasmisión vertical radica en lograr la supresión viral. Por ende, lo ideal es que la mujer comience su embarazo con una carga viral indetectable.

Los cambios en la terapia antirretroviral por fallo virológico típicamente conllevan pruebas de resistencia para dirigir la selección de una nueva terapia. Estas pruebas tardan generalmente unas cuatro semanas para ser procesadas. La ventana de tiempo durante un embarazo es finita y relativamente corta y, por ende, tener que hacer estas pruebas durante el embarazo quita tiempo valioso. Por eso, lo idóneo es realizar cualquier cambio de terapia antes de que la mujer quede embarazada. Además, realizar algún cambio en la terapia antirretroviral por alguna otra razón (poca tolerabilidad, potencial de efectos adversos durante el embarazo, etc.) debería ocurrir antes del embarazo.

En resumen, llevar a cabo una evaluación preconcepcional en una mujer con VIH ofrece el panorama ideal de comenzar un embarazo con una terapia antirretroviral segura y que logre la supresión viral.

Casos en que es mejor postergar la gestación

En algunas ocasiones, el resultado de la evaluación preconcepcional puede demostrar que la mujer no se encuentra en el momento idóneo para la gestación. En estos casos, resulta importante educar a la paciente sobre las razones por las cuales resulta necesario postergar un embarazo y establecer un plan de acción para atender a las mismas. Durante dicho proceso, se debe orientar a la mujer sobre los diferentes métodos anticonceptivos disponibles, sus riesgos, beneficios y efectos secundarios. Cabe recalcar que algunos métodos anticonceptivos pueden interactuar con algunos antirretrovirales afectando así la efectividad de ambas terapias. Las interacciones más significativas ocurren con los métodos con contenido estrogénico. También es importante tomar en cuenta la reversibilidad del método contraceptivo y que el mismo responda a las expectativas de tiempo que tenga la mujer para lograr un embarazo y su edad.

Comentario y sugerencias

Histórica y culturalmente, son pocas las mujeres que acuden a su médico de cabecera o ginecólogo y que explícitamente solicitan una evaluación preconcepcional o verbalizan su interés en un embarazo. Más aún, una gran proporción de los embarazos no son planificados. Queda a los proveedores de salud tornar cada visita rutinaria en una oportunidad para discutir los intereses reproductivos de sus pacientes con potencial reproductivo. Puede ser tan sencillo como hacer las siguientes preguntas: ¿estás activa sexualmente?, ¿está en tus planes a corto plazo buscar un embarazo?, ¿qué estás haciendo para evitarlo?

Integrar la visión del cuidado preconcepcional en el manejo rutinario de nuestras pacientes es definitivamente el punto de partida para un embarazo exitoso.

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The only single-pill regimen built with dolutegravir

- TRIUMEQ alone is not recommended for use in patients with current or past history of resistance to any components of TRIUMEQ
- TRIUMEQ alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor (INSTI) resistance because the dose of dolutegravir in TRIUMEQ is insufficient in these subpopulations. See full prescribing information for dolutegravir
- Coadministration of TRIUMEQ with efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin requires an additional dolutegravir 50-mg tablet, separated by 12 hours from TRIUMEQ

Not an actual patient.

Indications and Usage:

TRIUMEQ is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.

Limitations of Use:

- TRIUMEQ alone is not recommended for use in patients with current or past history of resistance to any components of TRIUMEQ
- TRIUMEQ alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected INSTI resistance because the dose of dolutegravir in TRIUMEQ is insufficient in these subpopulations. See full prescribing information for dolutegravir

Important Safety Information:

BOXED WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS B VIRUS (HBV): *See full Prescribing Information for complete boxed warning.*

Hypersensitivity Reactions:

- **Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir-containing products**
- **Hypersensitivity to abacavir is a multi-organ clinical syndrome**
- **Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with TRIUMEQ or reinitiation of therapy with TRIUMEQ unless patients have had an HLA-B*5701 allele assessment**
- **Discontinue TRIUMEQ as soon as hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue TRIUMEQ if hypersensitivity cannot be ruled out, even when other diagnoses are possible**
- **Following a hypersensitivity reaction to abacavir, NEVER restart TRIUMEQ or any other abacavir-containing product**

Lactic Acidosis and Severe Hepatomegaly:

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues**

Exacerbations of Hepatitis B:

- **Severe acute exacerbations of HBV have been reported in patients who are co-infected with HBV and HIV-1 and have discontinued lamivudine, a component of TRIUMEQ. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment**

CONTRAINDICATIONS

- Do not use in patients who have the HLA-B*5701 allele
- Do not use in patients with previous hypersensitivity reaction to abacavir, dolutegravir, or lamivudine
- Coadministration of TRIUMEQ with dofetilide (antiarrhythmic) is contraindicated due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events with concomitant use of dolutegravir
- Do not use in patients with moderate or severe hepatic impairment

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions to Dolutegravir:

- Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in <1% of subjects receiving TIVICAY® in Phase 3 clinical trials
- Clinically, it is not possible to determine whether a hypersensitivity reaction with TRIUMEQ would be caused by abacavir or dolutegravir. Discontinue TRIUMEQ and other suspect agents immediately if signs or symptoms of hypersensitivity reaction develop
- Never restart TRIUMEQ or any other abacavir- or dolutegravir-containing product in patients who have stopped therapy with TRIUMEQ due to a hypersensitivity reaction

Effects on Serum Liver Biochemistries in Patients with Hepatitis B or C Co-infection:

- Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TRIUMEQ. In some cases the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn
- Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TRIUMEQ are recommended in patients with underlying hepatic disease such as hepatitis B or C

Continued on next page.

For your HLA-B*5701–negative adult patients with HIV-1...

Triumeq®

abacavir 600 mg/dolutegravir 50 mg/ lamivudine 300 mg tablets

- 80% of patients taking TRIUMEQ achieved HIV-1 RNA <50 copies/mL compared with 72% taking Atripla® (EFV/TDF/FTC) in the SINGLE study at 96 weeks*
- 3% of patients taking TRIUMEQ discontinued due to adverse events compared with 12% taking Atripla in the SINGLE study at 96 weeks*
- TRIUMEQ does not require boosting and can be taken with or without food[1]

*Based on data from the SINGLE study, a randomized, double-blind, active-control trial comparing dolutegravir 50 mg once daily + EPZICOM® (ABC/3TC) (n=414) or EFV/TDF/FTC once daily (n=419) in treatment-naïve HLA-B*5701–negative adults.[2] Dolutegravir + ABC/3TC is bioequivalent to 1 TRIUMEQ tablet. At baseline, 32% of patients had HIV-1 RNA >100,000 copies/mL and 53% had $CD4^+$ T-cell counts <350 cells/mm^3.
EFV/TDF/FTC=efavirenz/tenofovir/emtricitabine; ABC/3TC=abacavir sulfate/lamivudine.

Scan or visit www.triumeq.com for more information.

Use With Interferon- and Ribavirin-based Regimens: Hepatic decompensation, some fatal, has occurred in HIV-1/hepatitis C virus (HCV) co-infected patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and TRIUMEQ should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation. Discontinue TRIUMEQ as medically appropriate.

Immune Reconstitution Syndrome: During the initial phase of treatment, immune reconstitution syndrome can occur, which may necessitate further evaluation and treatment. Autoimmune disorders have been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

Fat Redistribution: Redistribution/accumulation of body fat has been observed in patients receiving antiretroviral therapy.

Myocardial Infarction (MI):
- An observational study showed an increase in MI with abacavir; a sponsor-conducted, pooled analysis did not show increased risk. In totality, the available data are inconclusive
- The underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (eg, hypertension, hyperlipidemia, diabetes mellitus, smoking)

Use With Certain Antiretroviral Products: TRIUMEQ contains fixed doses of an INSTI (dolutegravir) and 2 nucleoside analogue reverse transcriptase inhibitors (abacavir and lamivudine), and should not be administered concomitantly with other products containing abacavir or lamivudine.

ADVERSE REACTIONS
- The most commonly reported (≥2%) adverse reactions of at least moderate intensity in treatment-naïve adult subjects receiving TRIUMEQ were insomnia (3%), headache (2%), and fatigue (2%)

DRUG INTERACTIONS
- Coadministration of TRIUMEQ with drugs that are strong inducers of UGT1A1 and/or CYP3A may result in reduced plasma concentrations of dolutegravir. Consult the full Prescribing Information for TRIUMEQ for more information
- Coadministration of TRIUMEQ with efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin requires an additional dolutegravir 50-mg tablet, separated by 12 hours from TRIUMEQ
- TRIUMEQ should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications. Alternatively, TRIUMEQ and supplements containing calcium or iron can be taken together with food

USE IN SPECIFIC POPULATIONS
- **Pregnancy:** Pregnancy Category C. TRIUMEQ should be used during pregnancy only if the potential benefit justifies the potential risk. An Antiretroviral Pregnancy Registry has been established
- **Breastfeeding:** Breastfeeding is NOT recommended due to the potential for HIV transmission and the potential for adverse reactions in nursing infants
- **Pediatric Patients:** Safety and effectiveness of TRIUMEQ in pediatric patients have not been established
- **Patients with Impaired Renal Function:** TRIUMEQ is not recommended in patients with creatinine clearance <50 mL per min
- **Patients with Impaired Hepatic Function:** If a dose reduction of abacavir, a component of TRIUMEQ, is required for patients with mild hepatic impairment, then the individual components should be used

References: 1. Min S, Song I, Borland J, et al. Pharmacokinetics and safety of S/GSK1349572, a next-generation HIV integrase inhibitor, in healthy volunteers. *Antimicrob Agents Chemother.* 2010;54(1):254-258. **2.** Walmsley SL, Antela AA, Clumeck N, et al; for the SINGLE Investigators. Dolutegravir plus abacavir–lamivudine for the treatment of HIV-1 infection. *N Engl J Med.* 2013;369:1807-1818.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for TRIUMEQ on the following pages.

BRIEF SUMMARY

TRIUMEQ® (abacavir, dolutegravir, and lamivudine) tablets, for oral use

The following is a brief summary only; see full prescribing information, including boxed warning, for complete product information.

WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS B

Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have been associated with abacavir, a component of TRIUMEQ®. Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele *[see Warnings and Precautions]*.

All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with TRIUMEQ or reinitiation of therapy with TRIUMEQ unless patients have had an HLA-B*5701 allele assessment. Discontinue TRIUMEQ if a hypersensitivity reaction is suspected. TRIUMEQ is contraindicated in patients who have the HLA-B*5701 allele or in patients with a prior hypersensitivity reaction to abacavir *[see Contraindications, Warnings and Precautions]*. Reintroduction of TRIUMEQ or any other abacavir-containing product can result in life-threatening or fatal hypersensitivity reactions, even in patients who have no history of hypersensitivity to abacavir therapy. Such reactions can occur within hours *[see Warnings and Precautions]*.

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, and other antiretrovirals. Discontinue TRIUMEQ if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions]*.

Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, one component of TRIUMEQ. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue TRIUMEQ and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions]*.

CONTRAINDICATIONS

TRIUMEQ is contraindicated in patients: who have the HLA-B*5701 allele *[see Warnings and Precautions]*; with previous hypersensitivity reaction to abacavir (Before starting TRIUMEQ, review medical history for prior exposure to any abacavir-containing product. NEVER restart TRIUMEQ or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status *[see Warnings and Precautions]*); with previous hypersensitivity reaction to dolutegravir *[see Warnings and Precautions]* or lamivudine; receiving dofetilide, due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events with concomitant use of dolutegravir *[see Drug Interactions]*; with moderate or severe hepatic impairment *[see Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reaction: Hypersensitivity reactions have been reported with the use of abacavir or dolutegravir, components of TRIUMEQ. Abacavir: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir-containing regimens. See full prescribing information for ZIAGEN® (abacavir). Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with abacavir or reinitiation of abacavir therapy unless HLA-B*5701 information is available. Do not treat HLA-B*5701-positive patients with an abacavir-containing regimen *[see Contraindications]*. HLA-B*5701-negative patients may develop a hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients. Regardless of HLA-B*5701 status, permanently discontinue TRIUMEQ if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Symptoms indicating a multi-organ clinical syndrome usually appear within the first 6 weeks of treatment with abacavir (median time to onset was 9 days), although the reaction may occur at any time during therapy. The reaction is typically characterized by the presentation of key signs or symptoms in 2 or more of the following groups: (1) fever; (2) rash; (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain); (4) constitutional (including generalized malaise, fatigue, or achiness); (5) respiratory (including dyspnea, cough, or pharyngitis). Other signs and symptoms of hypersensitivity include lethargy, headache, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), arthralgia, and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions. Physical findings associated with hypersensitivity to abacavir in some subjects include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash. Laboratory abnormalities associated with hypersensitivity to abacavir in some subjects include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia. *Clinical Management of Abacavir Hypersensitivity:* Discontinue TRIUMEQ as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue TRIUMEQ if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications). Following a hypersensitivity reaction to abacavir, NEVER restart TRIUMEQ or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death. When therapy with TRIUMEQ has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of TRIUMEQ or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of TRIUMEQ to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, DO NOT reintroduce TRIUMEQ or any other abacavir-containing product. If symptoms consistent with abacavir hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of TRIUMEQ or any other abacavir-containing product and that reintroduction of TRIUMEQ or introduction of any other abacavir-containing product needs to be undertaken only if medical care can be readily accessed by the patient or others. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision-making. Even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction. Dolutegravir: Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving TIVICAY® in Phase 3 clinical trials. Discontinue TRIUMEQ and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with TRIUMEQ or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. Clinically, it is not possible to determine whether a hypersensitivity reaction with TRIUMEQ would be caused by abacavir or dolutegravir. Therefore, never restart TRIUMEQ or any other abacavir- or dolutegravir-containing product in patients who have stopped therapy with TRIUMEQ due to a hypersensitivity reaction. **Lactic Acidosis and Severe Hepatomegaly with Steatosis:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. See full prescribing information for ZIAGEN (abacavir) and EPIVIR® (lamivudine). Treatment with TRIUMEQ should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). **Patients with Hepatitis B or C Virus Co-infection:** Effects on Serum Liver Biochemistries: Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TRIUMEQ *[see Adverse Reactions]*. See full prescribing information for TIVICAY (dolutegravir). In some cases the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TRIUMEQ are recommended in patients with underlying hepatic disease such as hepatitis B or C. Posttreatment exacerbations of Hepatitis: Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. See full prescribing information for EPIVIR (lamivudine). Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. Emergence of Lamivudine-resistant HBV: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV. Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. See full prescribing information for EPIVIR (lamivudine). **Use with Interferon- and Ribavirin-based Regimens:** Patients receiving interferon alfa with or without ribavirin and TRIUMEQ should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. See full prescribing information for EPIVIR (lamivudine). Discontinuation of TRIUMEQ should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6) (see full prescribing information for interferon and ribavirin). **Immune Reconstitution Syndrome:** Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TRIUMEQ. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment. **Fat Redistribution:** Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established. **Myocardial Infarction:** In a published prospective, observational, epidemiological trial designed to investigate the rate of myocardial infarction (MI) in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of MI. In a sponsor-conducted pooled analysis of clinical trials, no excess risk of MI was observed in abacavir-treated subjects as compared with control subjects. In totality, the available data from the observational cohort and from clinical trials are inconclusive. As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking). **Related Products that are Not Recommended:** TRIUMEQ contains fixed doses of an INSTI (dolutegravir) and 2 nucleoside analogue reverse transcriptase inhibitors (abacavir and lamivudine); concomitant administration of TRIUMEQ with other products containing abacavir or lamivudine is not recommended.

Continued on next page

BRIEF SUMMARY for TRIUMEQ® (abacavir, dolutegravir, and lamivudine) Tablets (cont'd)

ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling: Serious and sometimes fatal hypersensitivity reaction *[see Boxed Warning, Warnings and Precautions]*, Lactic acidosis and severe hepatomegaly *[see Boxed Warning, Warnings and Precautions]*, Effects on serum liver biochemistries in patients with hepatitis B or C co-infection *[see Warnings and Precautions]*, Exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions]*, Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C *[see Warnings and Precautions]*, Immune reconstitution syndrome *[see Warnings and Precautions]*, Fat redistribution *[see Warnings and Precautions*], Myocardial infarction *[see Warnings and Precautions]*.

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Treatment-emergent Adverse Drug Reactions (ADRs): The safety assessment of TRIUMEQ is primarily based on the analyses of data from a randomized, international, multicenter, double-blind, active-controlled trial, SINGLE (ING114467) and supported by data in treatment-experienced, INSTI-naïve subjects from SAILING (ING111762) and by data from other treatment-naïve trials. See full prescribing information for TIVICAY.

Treatment-naïve Subjects: In SINGLE, 833 adult subjects were randomized and received at least one dose of either dolutegravir (TIVICAY) 50 mg with fixed-dose abacavir sulfate and lamivudine (EPZICOM®) once daily (n = 414) or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA®) once daily (n = 419). Through 96 weeks, the rate of adverse events leading to discontinuation was 3% in subjects receiving TIVICAY + EPZICOM and 12% in subjects receiving ATRIPLA once daily. Treatment-emergent ADRs of moderate to severe intensity observed in at least 2% of subjects in either treatment arm of SINGLE are provided in Table 2.

Table 2. Treatment-emergent Adverse Drug Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-naïve Subjects in SINGLE (Week 96 Analysis)

Adverse Reaction	TIVICAY + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
Psychiatric		
Insomnia	3%	2%
Depression	1%	2%
Abnormal dreams	<1%	2%
Nervous System		
Dizziness	<1%	5%
Headache	2%	2%
Gastrointestinal		
Nausea	<1%	3%
Diarrhea	<1%	2%
General Disorders		
Fatigue	2%	2%
Skin and Subcutaneous Tissue		
Rash[a]	<1%	6%
Ear and Labyrinth		
Vertigo	0	2%

[a] Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

Treatment-experienced Subjects: SAILING is an international, double-blind trial in INSTI-naïve, antiretroviral treatment-experienced adult subjects. Subjects were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rate of adverse events leading to discontinuation was consistent with that seen in the overall treatment-naïve patient population. See full prescribing information for TIVICAY. The ADRs observed in the subset of subjects who received TIVICAY + EPZICOM were generally consistent with those seen in the overall treatment-naïve patient population. Less Common Adverse Reactions Observed in Clinical Trials: The following adverse reactions occurred in less than 2% of treatment-naïve or treatment-experienced subjects in any one trial. These events have been included because of their seriousness and/or assessment of potential causal relationship. *Gastrointestinal Disorders:* Abdominal pain, abdominal distention, abdominal discomfort, dyspepsia, flatulence, gastroesophageal reflux disease, upper abdominal pain, vomiting. *General Disorders:* Fever, lethargy. *Hepatobiliary Disorders:* Hepatitis. *Metabolism and Nutrition Disorders:* Anorexia, hypertriglyceridemia. *Musculoskeletal Disorders:* Arthralgia, myositis. *Nervous:* Somnolence. *Psychiatric:* Nightmare and sleep disorder. *Renal and Urinary Disorders:* Renal impairment. *Skin and Subcutaneous Tissue Disorders:* Pruritus. Laboratory Abnormalities: *Treatment-naïve Subjects:* Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects in SINGLE are presented in Table 3. The mean change from baseline observed for selected lipid values is presented in Table 4.

Table 3. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-naïve Subjects in SINGLE (Week 96 Analysis)

Laboratory Abnormality	TIVICAY + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
ALT		
Grade 2 (>2.5-5.0 x ULN)	2%	5%
Grade 3 to 4 (>5.0 x ULN)	<1%	<1%
AST		
Grade 2 (>2.5-5.0 x ULN)	3%	3%
Grade 3 to 4 (>5.0 x ULN)	<1%	3%
Creatine kinase		
Grade 2 (6.0-9.9 x ULN)	4%	1%
Grade 3 to 4 (≥10.0 x ULN)	5%	7%
Hyperglycemia		
Grade 2 (126-250 mg/dL)	7%	5%
Grade 3 (>250 mg/dL)	2%	<1%
Lipase		
Grade 2 (>1.5-3.0 x ULN)	9%	9%
Grade 3 to 4 (>3.0 ULN)	4%	3%
Total neutrophils		
Grade 2 (0.75-0.99 x 10^9)	3%	5%
Grade 3 to 4 (<0.75 x 10^9)	2%	3%

ULN = Upper limit of normal.

Table 4. Mean Change from Baseline in Fasted Lipid Values in Treatment-naïve Subjects in SINGLE (Week 96 Analysis[a])

Lipid	TIVICAY + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
Cholesterol (mg/dL)	23.2	28.0
HDL cholesterol (mg/dL)	5.2	7.4
LDL cholesterol (mg/dL)	14.5	18.0
Triglycerides (mg/dL)	17.2	17.4

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (TIVICAY n = 30 and ATRIPLA n = 27). Fifty-five subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (SINGLE: TIVICAY n = 25 and ATRIPLA: n = 30).

Treatment-experienced Subjects: Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve trials. Hepatitis C Virus Co-infection: In SINGLE, the pivotal Phase 3 trial, subjects with hepatitis C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal; subjects with hepatitis B co-infection were excluded. Overall, the safety profile in subjects with hepatitis C virus co-infection was similar to that observed in subjects without hepatitis C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis C virus co-infection for both treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis C co-infected compared with HIV mono-infected subjects receiving TRIUMEQ were observed in 15% and 2% (vs. 24% and 4% of subjects treated with ATRIPLA), respectively *[see Warnings and Precautions]*. See also full prescribing information for TIVICAY. *Changes in Serum Creatinine:* Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2) of the full Prescribing Information]*. Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 24 to 96 weeks. In SINGLE, a mean change from baseline of 0.14 mg per dL (range: -0.32 mg per dL to 0.59 mg per dL) was observed after 96 weeks of treatment. Creatinine increases were similar in treatment-experienced subjects. Abacavir Sulfate and Lamivudine: Laboratory abnormalities observed in clinical trials of ZIAGEN (in combination with other antiretroviral treatment) were anemia, neutropenia, liver function test abnormalities, and elevations of CPK, blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical trials of EPIVIR (in combination with other antiretroviral treatment) were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase. **Postmarketing Experience:** In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Abacavir and/or Lamivudine: *Digestive:* Stomatitis. *Gastrointestinal:* Pancreatitis. *General:* Weakness. *Blood and Lymphatic Systems:* Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly. *Hypersensitivity:* Sensitization reactions (including anaphylaxis), urticaria. *Metabolism and Nutrition Disorders:* Hyperlactemia. *Musculoskeletal:* Muscle weakness, CPK elevation, rhabdomyolysis. *Nervous:* Paresthesia, peripheral neuropathy, seizures. *Respiratory:* Abnormal breath sounds/wheezing. *Skin:* Alopecia, erythema multiforme. Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

DRUG INTERACTIONS

Effect of Dolutegravir on the Pharmacokinetics of Other Agents: In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 µM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 µM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin) *[see Contraindications, Drug Interactions]*. In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC_{50} = 2.12 µM) and OAT3 (IC_{50} = 1.97 µM). However, in vivo, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3. In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 µM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, or multidrug resistance protein (MRP)2, or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6, CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the

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DRUG INTERACTIONS cont'd

pharmacokinetics of drugs that are substrates of these enzymes or transporters. In drug interaction trials, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following drugs: tenofovir, methadone, midazolam, rilpivirine, and oral contraceptives containing norgestimate and ethinyl estradiol. Using cross-study comparisons to historical pharmacokinetic data for each interacting drug, dolutegravir did not appear to affect the pharmacokinetics of the following drugs: atazanavir, darunavir, efavirenz, etravirine, fosamprenavir, lopinavir, ritonavir, and telaprevir. **Effect of Other Agents on the Pharmacokinetics of Dolutegravir:** Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir. Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations. Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 5) *[see Drug Interactions, also see Clinical Pharmacology (12.3) of the full Prescribing Information]*. Darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, tenofovir, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole had no clinically significant effect on the pharmacokinetics of dolutegravir. **Established and Other Potentially Significant Drug Interactions:** There were no drug-drug interaction trials conducted with the abacavir, dolutegravir, and lamivudine fixed-dose combination tablets. Information regarding potential drug interactions with dolutegravir (Table 5) and abacavir are provided below. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. *[See Clinical Pharmacology (12.3) of the full Prescribing Information]*.

Table 5. Established and Other Potentially Significant Drug Interactions for Dolutegravir: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓Dolutegravir	Use of TRIUMEQ with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from TRIUMEQ.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with TRIUMEQ because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional dolutegravir 50-mg dose should be taken, separated by 12 hours from TRIUMEQ.
Other Agents		
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with TRIUMEQ because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives; Sucralfate Buffered medications	↓Dolutegravir	Administer TRIUMEQ 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium and iron supplements, including multivitamins containing calcium or iron[a]	↓Dolutegravir	Administer TRIUMEQ 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, TRIUMEQ and supplements containing calcium or iron can be taken together with food.
Metformin	↑Metformin	Consider metformin dose reductions when coadministered with TRIUMEQ.
Rifampin[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from TRIUMEQ.

[a] *See Clinical Pharmacology (12.3) Table 9 of the full Prescribing Information for magnitude of interaction.*

Ethanol: *Abacavir:* Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure *[see Clinical Pharmacology (12.3) of the full Prescribing Information]*. Methadone: *Abacavir:* The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C. There are no adequate and well-controlled trials in pregnant women. Reproduction studies with the components of TRIUMEQ have been performed in animals. Animal reproduction studies are not always predictive of human response. TRIUMEQ should be used during pregnancy only if the potential benefit outweigh the risks. Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to TRIUMEQ or other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263. **Nursing Mothers:** The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, instruct **mothers not to breastfeed.** Dolutegravir: Studies in lactating rats and their offspring indicate that dolutegravir was present in rat milk. It is not known whether dolutegravir is excreted in human breast milk. Abacavir: Abacavir is excreted in the milk of lactating rats. Lamivudine: Lamivudine is excreted in human breast milk. **Pediatric Use:** Safety and effectiveness of TRIUMEQ in pediatric patients have not been established *[see Clinical Pharmacology (12.3) of the full Prescribing Information]*. **Geriatric Use:** Clinical trials of abacavir, dolutegravir, or lamivudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of TRIUMEQ in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3) of the full Prescribing Information]*. **Patients with Impaired Renal Function:** TRIUMEQ is not recommended for patients with impaired renal function (creatinine clearance less than 50 mL per min) because TRIUMEQ is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of TRIUMEQ, is required for patients with creatinine clearance less than 50 mL per min, then the individual components should be used *[see Clinical Pharmacology (12.3) of the full Prescribing Information]*. **Patients with Impaired Hepatic Function:** TRIUMEQ is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of abacavir, a component of TRIUMEQ, is required for patients with mild hepatic impairment (Child-Pugh Score A), then the individual components should be used *[see Clinical Pharmacology (12.3) of the full Prescribing Information]*. The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate (Child-Pugh Score B) or severe (Child-Pugh Score C) hepatic impairment; therefore, TRIUMEQ is contraindicated in these patients.

OVERDOSAGE

There is no known specific treatment for overdose with TRIUMEQ. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. Dolutegravir: As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis. Abacavir: It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis. Lamivudine: Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity: *Dolutegravir:* Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 26-fold higher than those in humans at the recommended dose of 50 mg once daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 17-fold and 30- fold higher in males and females, respectively, than those in humans at the recommended dose of 50 mg once daily. *Abacavir:* Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 7 to 28 times the human exposure at the recommended dose of 600 mg. *Lamivudine:* Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 12 times (mice) and 57 times (rats) the human exposures at the recommended dose of 300 mg. Mutagenicity: *Dolutegravir:* Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay. *Abacavir:* Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation. *Lamivudine:* Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver. Impairment of Fertility: Dolutegravir, abacavir, or lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 44, 9, or 112 times (respectively) higher than the exposures in humans at the doses of 50 mg, 600 mg, and 300 mg (respectively).

PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide).

Manufactured for:
ViiV Healthcare
ViiV Healthcare
Research Triangle Park, NC 27709

by:
GlaxoSmithKline
GlaxoSmithKline
Research Triangle Park, NC 27709

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Lamivudine is manufactured under agreement from **Shire Pharmaceuticals Group plc,** Basingstoke, UK

Tratamiento del VIH:
Estudios clínicos vs. el mundo real

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Observaciones y controversia

La proporción de personas que viven con VIH en un tratamiento exitoso es aparentemente más baja en el mundo real cuando se compara con los resultados de los estudios clínicos.

En otras palabras, "el mundo real no es tan color de rosa como lo pintan los estudios clínicos". En la última conferencia *IDWeek* (San Diego, CA, inicios de octubre de 2015), el Dr. Yunfeng Tie presentó datos de un análisis seccional-cruzado preparado en *Centers for Disease Control and Prevention* (CDC) donde se describe que un 92% de las personas diagnosticadas con VIH recibe una prescripción para terapia con antirretrovirales. Sin embargo, solo la mitad de ellos recibe alguno de los regímenes recomendados por las guías de tratamiento de VIH del Departamento de Salud de los Estados Unidos (DHHS).

Datos presentados:
- Un 92% recibió una prescripción para tratamiento antirretroviral;
- Un 80% mostró supresión viral en su última visita;
- Un 66% presentó supresión duradera (estudios clínicos > 80% / 48 semanas);
- Un 84% refirió adherencia (autorreporte); y
- Un 16% reportó efectos adversos (autorreporte).

Los datos presentados, en base a un proyecto de monitoreo médico (MMP), son parte del continuo sistema de vigilancia de CDC donde el muestreo debe ser una representación nacional. Los investigadores recolectan datos sociodemográficos y de comportamiento, por entrevistas y por información del récord médico.

Los datos de mayor interés son la supresión viral (conteo por debajo de 200c/ml) en la última visita médica, la duración de la supresión, la adherencia a los medicamentos y los efectos adversos a los mismos.

Discusión

Como ya se ha mencionado, cerca de un 52% de los pacientes estaban en una terapia recomendada por las guías del Departamento de Salud de los Estados Unidos (DHHS). Es también de sumo interés que el 76% de las personas que estaban tomando medicamentos recomendados tenían supresión viral duradera y que las personas con peores resultados no estaban recibiendo las terapias recomendadas.

La presentación reconoce, además de los comentarios de los participantes, que el estudio tiene variables y factores que pueden generar confusión: participaban personas que no estaban empezando tratamiento y las guías de tratamiento de VIH se han ido actualizando continuamente.

Los expertos opinaron también que los datos tienen mayor valor descriptivo sobre los medicamentos que están tomado las personas que viven con VIH y no tanto sobre cuán bien lo están haciendo.

Comentario

El mensaje que se quiere dar aquí es que los datos de mundo real nos ayudan a ver con mayor claridad cuál es el panorama en la lucha contra el VIH y también a entender mejor el desarrollo y la evolución en el cuidado de nuestros pacientes afectados por este virus.

Nuevos medicamentos en el horizonte para tratar VIH

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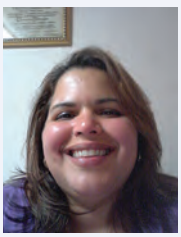

Actualmente hay 28 medicamentos en el mercado aprobados por la FDA para el tratamiento de VIH. Pero siempre hay espacio para mejorar. En la convención de ICAAC 2015 se discutieron nuevos medicamentos que están en estudio para poder estar en el mercado en un futuro cercano, algunos bajo clases ya existentes y otros como nuevas clases. Hablaremos sobre los 5 más cercanos a salir al mercado.

NRTI (nucleótidos inhibidores de la transcriptasa reversa): TAF (tenofovir alafenomide)

Es una propuesta mejorada del medicamento conocido como TDF (tenofovir disoproxil fumarate). TAF tendrá menor toxicidad renal y ósea a largo plazo. Actualmente se hacen estudios para probar la no inferioridad de TAF vs. TDF. Por esto la FDA decidió que en noviembre de 2015 se verá una nueva formulación de elvitegravir, cobicistat, emtricitabina, tenofovir (*Stribild*) utilizando TAF y, para abril de 2016, se espera la nueva formulación de tenofovir/emtricitabina (*Truvada*).

NNRTI (no nucleótidos inhibidores de la transcriptasa reversa): Doravirine

En esta clase había una gran necesidad pues se requería un medicamento con menos toxicidad, más tolerabilidad, buena barrera genética y pocas interacciones con otros fármacos. Este ha logrado todo esto y, además, ser potente en dosis bajas y con pocos efectos secundarios al compararse con efavirenz.

Inhibidores de Integrasa: Cabotegravir

Esta es la era de los inhibidores de integrasa, como se puede apreciar en las guías de tratamiento. Estos medicamentos pueden tener grandes beneficios con dosis y frecuencia menores. Cabotegravir es muy similar a la estructura de dolutegravir, tiene un perfil de resistencia similar y es potente en dosis bajas. Lo que destacable en este medicamento es que sobresale entre los que ya se conocen por su formulación, la cual es nanotecnología (por lo que tiene una vida media de 21 a 50 días). Esto ayuda a administrarlo en dosis mensuales o de cada 3 meses por vía subcutánea o intramuscular. Además, los estudios revelan que la reacción en el área de inyección es mínima.

Se viene estudiando tanto para tratamiento de prevención como de mantenimiento. En el estudio LATTE se evalúa si al ser tomado con rilpivirina de larga duración puede ser utilizado como terapia de mantenimiento inyectable.

CD4 attachment inhibitor: BMS-663068

Esta es una clase nueva de medicamento que provee un nuevo mecanismo de acción, muy importante en pacientes con múltiples resistencias. La entrada del virus a la

célula de CD4 consta de 3 pasos; hoy hay dos medicamentos que trabajan en dos de los pasos. Para el paso principal (cuando el virus se adhiere al CD4) no teníamos nada. Este medicamento inhibe la adherencia de CD4 a la proteína gp120 del VIH. Los datos de su farmacocinética indican que se podría dar una o dos veces al día. Aún se están llevando a cabo estudios para probar su efectividad.

Maturator inhibitor (inhibidor de maduración)

Esta nueva clase proveerá un nuevo mecanismo de acción. Después de ser infectado el CD4, el VIH crea copias nuevas del virus, donde la etapa final es la maduración del virus para seguir infectando otras células. Este tratamiento inhibirá el paso de maduración del virus. Si bien los estudios aún se llevan a cabo (BMS-955176), los resultados iniciales han demostrado una buena actividad antirretroviral, siendo la data aún insuficiente.

Comentario

Podemos pensar que en el horizonte tenemos nuevos tratamientos, más potentes y menos tóxicos para ser utilizados con dosis más bajas y menos frecuencia. Esto nos lleva a preguntarnos si podremos acariciar la idea de la cura VIH en un futuro cercano.